```
=> file medline
FILE 'MEDLINE' ENTERED AT 17:40:20 ON 12 MAY 2003

 FILE LAST UPDATED: 9 MAY 2003 (20030509/UP).  FILE COVERS 1958 TO DATE.

 On April 13, 2003, MEDLINE was reloaded.  See HELP RLOAD for details.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2003 vocabulary.  See http://www.nlm.nih.gov/mesh/changes2003.html
 for a description on changes.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.
```

CT = controlled terminology

```
=> d que l4

L1          2731 SEA FILE=MEDLINE ABB=ON  PLU=ON  CYCLODEXTRINS/CT
L2           118 SEA FILE=MEDLINE ABB=ON  PLU=ON  L1 AND (EVAP? OR DEHYDRAT? OR
                 DRY OR DRIED OR DRYING)
L3            55 SEA FILE=MEDLINE ABB=ON  PLU=ON  L1 AND (HYDRAT? OR REHYDRAT?
                 OR WET OR WETTED OR WETTING OR DISSOLV?(5A)(AQUEOUS OR WATER
                 OR H2O))
L4            12 SEA FILE=MEDLINE ABB=ON  PLU=ON  L2 AND L3
```

12 cites for medline

```
=> file drugu

FILE 'DRUGU' ENTERED AT 17:40:22 ON 12 MAY 2003
COPYRIGHT (C) 2003 THOMSON DERWENT

FILE LAST UPDATED: 7 MAY 2003       <20030507/UP>
>>>  DERWENT DRUG FILE (SUBSCRIBER)  <<<

>>>  SDI'S MAY BE RUN WEEKLY OR MONTHLY AS OF JUNE 2001.  <<<
>>>  (WEEKLY IS THE DEFAULT). FOR PRICING INFORMATION     <<<
>>>  SEE HELP COST                                        <<<

>>>  FILE COVERS 1983 TO DATE  <<<
>>>  THESAURUS AVAILABLE IN /CT  <<<


=> d que l74

L70         2272 SEA FILE=DRUGU ABB=ON  PLU=ON  .BETA.CYCLODEXTRIN
L71          318 SEA FILE=DRUGU ABB=ON  PLU=ON  L70 AND (EVAP? OR DEHYDRAT? OR
                 DRY OR DRIED OR DRYING)
L72          106 SEA FILE=DRUGU ABB=ON  PLU=ON  L70 AND (HYDRAT? OR REHYDRAT?
                 OR WET OR WETTED OR WETTING OR DISSOLV?(5A)(AQUEOUS OR WATER
                 OR H2O))
L73           46 SEA FILE=DRUGU ABB=ON  PLU=ON  L71 AND L72
L74            4 SEA FILE=DRUGU ABB=ON  PLU=ON  L73 AND (COMPACTIBILITY OR
                 BINDING OR DEHYDRATED)/TI
```

4 cites

```
=> d que l77

L70         2272 SEA FILE=DRUGU ABB=ON  PLU=ON  .BETA.CYCLODEXTRIN
L76            6 SEA FILE=DRUGU ABB=ON  PLU=ON  L70 AND BED
L77            1 SEA FILE=DRUGU ABB=ON  PLU=ON  L76 AND OPTIMIZATION/TI
```

1 cite

=> s l74 or l77

L233 5 L74 OR L77 5 cites for Drugs

=> file biosis

FILE 'BIOSIS' ENTERED AT 17:40:25 ON 12 MAY 2003

FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 7 May 2003 (20030507/ED)

=> d que l61

L57 4461 SEA FILE=BIOSIS ABB=ON PLU=ON .BETA.CYCLODEXTRIN
L58 81 SEA FILE=BIOSIS ABB=ON PLU=ON L57 AND (HYDRAT? OR REHYDRAT? OR WET OR WETTED OR WETTING OR DISSOLV?(5A)(AQUEOUS OR WATER OR H2O))
L59 179 SEA FILE=BIOSIS ABB=ON PLU=ON L57 AND (EVAP? OR DEHYDRAT? OR DRY OR DRIED OR DRYING)
L60 23 SEA FILE=BIOSIS ABB=ON PLU=ON L58 AND L59
L61 3 SEA FILE=BIOSIS ABB=ON PLU=ON L60 AND (CRYSTALLINITY CHANGES OR FAST OR FLUIDIZ?)/TI 3 cites

=> d que l63

L57 4461 SEA FILE=BIOSIS ABB=ON PLU=ON .BETA.CYCLODEXTRIN
L58 81 SEA FILE=BIOSIS ABB=ON PLU=ON L57 AND (HYDRAT? OR REHYDRAT? OR WET OR WETTED OR WETTING OR DISSOLV?(5A)(AQUEOUS OR WATER OR H2O))
L62 262 SEA FILE=BIOSIS ABB=ON PLU=ON L57 AND (?PARTICL? OR ?SPHER? OR SIZE)
L63 10 SEA FILE=BIOSIS ABB=ON PLU=ON L62 AND L58 10 cites

=> d que l66

L57 4461 SEA FILE=BIOSIS ABB=ON PLU=ON .BETA.CYCLODEXTRIN
L59 179 SEA FILE=BIOSIS ABB=ON PLU=ON L57 AND (EVAP? OR DEHYDRAT? OR DRY OR DRIED OR DRYING)
L62 262 SEA FILE=BIOSIS ABB=ON PLU=ON L57 AND (?PARTICL? OR ?SPHER? OR SIZE)
L65 29 SEA FILE=BIOSIS ABB=ON PLU=ON L62 AND L59
L66 1 SEA FILE=BIOSIS ABB=ON PLU=ON L65 AND POWDER PROPERTIES/TI 1 cite

=> s l61 or l63 or l66

L234 14 L61 OR L63 OR L66 14 cites for Biosis

=> file biotechno

FILE 'BIOTECHNO' ENTERED AT 17:40:29 ON 12 MAY 2003

```
FILE LAST UPDATED: 8 MAY 2003       <20030508/UP>
FILE COVERS 1980 TO DATE.

>>>  SIMULTANEOUS LEFT AND RIGHT TRUNCATION AVAILABLE IN
     /CT AND BASIC INDEX  <<<

=> d que l53

L49          645 SEA FILE=BIOTECHNO ABB=ON  PLU=ON  .BETA.CYCLODEXTRIN
L50            7 SEA FILE=BIOTECHNO ABB=ON  PLU=ON  L49 AND (HYDRAT? OR
                 REHYDRAT? OR WET OR WETTED OR WETTING OR DISSOLV?(5A)(AQUEOUS
                 OR WATER OR H2O))
L51           30 SEA FILE=BIOTECHNO ABB=ON  PLU=ON  L49 AND (EVAP? OR DEHYDRAT?
                 OR DRY OR DRIED OR DRYING)
L52            4 SEA FILE=BIOTECHNO ABB=ON  PLU=ON  L50 AND L51
L53            1 SEA FILE=BIOTECHNO ABB=ON  PLU=ON  L52 AND AMBIENT/TI
```

I cite for Biotechno

```
=> file uspatful

FILE 'USPATFULL' ENTERED AT 17:40:30 ON 12 MAY 2003
CA INDEXING COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)

FILE COVERS 1971 TO PATENT PUBLICATION DATE: 8 May 2003 (20030508/PD)
FILE LAST UPDATED: 8 May 2003 (20030508/ED)
HIGHEST GRANTED PATENT NUMBER: US6560778
HIGHEST APPLICATION PUBLICATION NUMBER: US2003088899
CA INDEXING IS CURRENT THROUGH 8 May 2003 (20030508/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 8 May 2003 (20030508/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Feb 2003
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Feb 2003

>>>  USPAT2 is now available.  USPATFULL contains full text of the     <<<
>>>  original, i.e., the earliest published granted patents or         <<<
>>>  applications.  USPAT2 contains full text of the latest US         <<<
>>>  publications, starting in 2001, for the inventions covered in     <<<
>>>  USPATFULL.  A USPATFULL record contains not only the original     <<<
>>>  published document but also a list of any subsequent              <<<
>>>  publications.  The publication number, patent kind code, and      <<<
>>>  publication date for all the US publications for an invention     <<<
>>>  are displayed in the PI (Patent Information) field of USPATFULL   <<<
>>>  records and may be searched in standard search fields, e.g., /PN, <<<
>>>  /PK, etc.                                                         <<<

>>>  USPATFULL and USPAT2 can be accessed and searched together        <<<
>>>  through the new cluster USPATALL.  Type FILE USPATALL to          <<<
>>>  enter this cluster.                                               <<<
>>>                                                                    <<<
>>>  Use USPATALL when searching terms such as patent assignees,       <<<
>>>  classifications, or claims, that may potentially change from     <<<
>>>  the earliest to the latest publication.                           <<<

This file contains CAS Registry Numbers for easy and accurate
substance identification.

=> d que l229

L224        3104 SEA FILE=USPATFULL ABB=ON  PLU=ON  .BETA.CYCLODEXTRIN
L225         232 SEA FILE=USPATFULL ABB=ON  PLU=ON  L224(10A) (EVAP? OR
```

```
                DEHYDRAT? OR DRY OR DRIED OR DRYING)
L226          216 SEA FILE=USPATFULL ABB=ON  PLU=ON  L224(10A) (HYDRAT? OR
                REHYDRAT? OR WET OR WETTED OR WETTING OR DISSOLV?(5A)(AQUEOUS
                OR WATER OR H2O))
L227           46 SEA FILE=USPATFULL ABB=ON  PLU=ON  L225 AND L226
L228           16 SEA FILE=USPATFULL ABB=ON  PLU=ON  L227 AND (COMPRESS? OR
                COMPACT?)
L229            1 SEA FILE=USPATFULL ABB=ON  PLU=ON  L228 AND IMPROVED DISSOLUTIO
                N/TI
```

1 patent

```
=> d que l232

L224        3104 SEA FILE=USPATFULL ABB=ON  PLU=ON  .BETA.CYCLODEXTRIN
L225         232 SEA FILE=USPATFULL ABB=ON  PLU=ON  L224(10A) (EVAP? OR
                DEHYDRAT? OR DRY OR DRIED OR DRYING)
L226         216 SEA FILE=USPATFULL ABB=ON  PLU=ON  L224(10A) (HYDRAT? OR
                REHYDRAT? OR WET OR WETTED OR WETTING OR DISSOLV?(5A)(AQUEOUS
                OR WATER OR H2O))
L227          46 SEA FILE=USPATFULL ABB=ON  PLU=ON  L225 AND L226
L230          13 SEA FILE=USPATFULL ABB=ON  PLU=ON  L227 AND BED
L231           6 SEA FILE=USPATFULL ABB=ON  PLU=ON  L230 AND FLUIDI?
L232           1 SEA FILE=USPATFULL ABB=ON  PLU=ON  L231 AND FGF

=> s l229 or l232

L235           2 L229 OR L232
```

1 patent

2 patents for USPATFULL

```
=> file hcaplus

FILE 'HCAPLUS' ENTERED AT 17:40:33 ON 12 MAY 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)

Copyright of the articles to which records in this database refer is
held by the publishers listed in the PUBLISHER (PB) field (available
for records published or updated in Chemical Abstracts after December
26, 1996), unless.otherwise indicated in the original publications.
The CA Lexicon is the copyrighted intellectual property of the
the American Chemical Society and is provided to assist you in searching
databases on STN.  Any dissemination, distribution, copying, or storing
of this information, without the prior written consent of CAS, is
strictly prohibited.

FILE COVERS 1907 - 12 May 2003  VOL 138 ISS 20
FILE LAST UPDATED: 11 May 2003  (20030511/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.
```

PFT = old, new & used for terms

OBI = all fields except the abstract

```
=> d que l142

L120(      13341)SEA FILE=HCAPLUS ABB=ON  PLU=ON  7585-39-9/RN OR .BETA.CYCLODEX
                 TRIN/OBI
L121(      14976)SEA FILE=HCAPLUS ABB=ON  PLU=ON  EVAPORATION+PFT/CT
L122(        423)SEA FILE=HCAPLUS ABB=ON  PLU=ON  DESOLVATION+PFT/CT
```

NT= narrower term

```
L123(     14976)SEA FILE=HCAPLUS ABB=ON  PLU=ON  EVAPORATION+PFT/CT
L124(     31424)SEA FILE=HCAPLUS ABB=ON  PLU=ON  DRYING+PFT,NT/CT
L125(         5)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L120 AND L121
L126(         2)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L120 AND L122
L127(         5)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L120 AND L123
L128(       145)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L120 AND L124
L129(       149)SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L125 OR L126 OR L127 OR
                L128)
L130(      9466)SEA FILE=HCAPLUS ABB=ON  PLU=ON  WETTING+PFT/CT
L131(      6163)SEA FILE=HCAPLUS ABB=ON  PLU=ON  WETTABILITY+PFT/CT
L132(     21063)SEA FILE=HCAPLUS ABB=ON  PLU=ON  HYDRATION/CT
L133(      2249)SEA FILE=HCAPLUS ABB=ON  PLU=ON  HYDRATES/CT
L134(     48287)SEA FILE=HCAPLUS ABB=ON  PLU=ON  PARTICLE SIZE+PFT/CT
L135(      9612)SEA FILE=HCAPLUS ABB=ON  PLU=ON  PARTICLE SIZE DISTRIBUTION+PFT
                /CT
L136(        50)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L120 AND (L130 OR L131 OR
                L132)
L137(         4)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L120 AND L133
L138(        91)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L120 AND (L134 OR L135)
L139(         1)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L129 AND (L136 OR L137)
L140(      5335)SEA FILE=HCAPLUS ABB=ON  PLU=ON  SOLUBILIZATION/CT
L141(        33)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L129 AND L140
L142          1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L138 AND (L139 OR L141)
```

1 cite

```
=> d que l165

L143(     13341)SEA FILE=HCAPLUS ABB=ON  PLU=ON  7585-39-9/RN OR .BETA.CYCLODEX
                TRIN/OBI
L144(     14976)SEA FILE=HCAPLUS ABB=ON  PLU=ON  EVAPORATION+PFT/CT
L145(       423)SEA FILE=HCAPLUS ABB=ON  PLU=ON  DESOLVATION+PFT/CT
L146(     14976)SEA FILE=HCAPLUS ABB=ON  PLU=ON  EVAPORATION+PFT/CT
L147(     31424)SEA FILE=HCAPLUS ABB=ON  PLU=ON  DRYING+PFT,NT/CT
L148(         5)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L143 AND L144
L149(         2)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L143 AND L145
L150(         5)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L143 AND L146
L151(       145)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L143 AND L147
L152(       149)SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L148 OR L149 OR L150 OR
                L151)
L153(      9466)SEA FILE=HCAPLUS ABB=ON  PLU=ON  WETTING+PFT/CT
L154(      6163)SEA FILE=HCAPLUS ABB=ON  PLU=ON  WETTABILITY+PFT/CT
L155(     21063)SEA FILE=HCAPLUS ABB=ON  PLU=ON  HYDRATION/CT
L156(      2249)SEA FILE=HCAPLUS ABB=ON  PLU=ON  HYDRATES/CT
L157(     10093)SEA FILE=HCAPLUS ABB=ON  PLU=ON  COMPRESSION+PFT/CT
L158(      8759)SEA FILE=HCAPLUS ABB=ON  PLU=ON  COMPRESSIBILITY+PFT/CT
L159(        50)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L143 AND (L153 OR L154 OR
                L155)
L160(         4)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L143 AND L156
L161(        23)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L143 AND (L157 OR L158)
L162(         1)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L152 AND (L159 OR L160)
L163(      5335)SEA FILE=HCAPLUS ABB=ON  PLU=ON  SOLUBILIZATION/CT
L164(        33)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L152 AND L163
L165          1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L161 AND (L162 OR L164)
```

1 cite

```
=> d que l187

L166(     13341)SEA FILE=HCAPLUS ABB=ON  PLU=ON  7585-39-9/RN OR .BETA.CYCLODEX
                TRIN/OBI
L167(     14976)SEA FILE=HCAPLUS ABB=ON  PLU=ON  EVAPORATION+PFT/CT
```

```
L168(       423)SEA FILE=HCAPLUS ABB=ON  PLU=ON  DESOLVATION+PFT/CT
L169(     14976)SEA FILE=HCAPLUS ABB=ON  PLU=ON  EVAPORATION+PFT/CT
L170(     31424)SEA FILE=HCAPLUS ABB=ON  PLU=ON  DRYING+PFT,NT/CT
L171(      9466)SEA FILE=HCAPLUS ABB=ON  PLU=ON  WETTING+PFT/CT
L172(      6163)SEA FILE=HCAPLUS ABB=ON  PLU=ON  WETTABILITY+PFT/CT
L173(     21063)SEA FILE=HCAPLUS ABB=ON  PLU=ON  HYDRATION/CT
L174(      2249)SEA FILE=HCAPLUS ABB=ON  PLU=ON  HYDRATES/CT
L175(     48287)SEA FILE=HCAPLUS ABB=ON  PLU=ON  PARTICLE SIZE+PFT/CT
L176(      9612)SEA FILE=HCAPLUS ABB=ON  PLU=ON  PARTICLE SIZE DISTRIBUTION+PFT
                 /CT
L177(     10093)SEA FILE=HCAPLUS ABB=ON  PLU=ON  COMPRESSION+PFT/CT
L178(      8759)SEA FILE=HCAPLUS ABB=ON  PLU=ON  COMPRESSIBILITY+PFT/CT
L179(        91)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L166 AND (L175 OR L176)
L180(        23)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L166 AND (L177 OR L178)
L181(        64)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L166(L)(GRANUL? OR PELLET?)
L182(      5335)SEA FILE=HCAPLUS ABB=ON  PLU=ON  SOLUBILIZATION/CT
L183(      9138)SEA FILE=HCAPLUS ABB=ON  PLU=ON  SIZE REDUCTION+PFT/CT
L184(        34)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L166 AND L183
L185(        20)SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L184 OR (L179 OR L180 OR
                 L181)) AND ((L171 OR L172 OR L173 OR L174) OR L182)
L186(        17)SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L184 OR (L179 OR L180 OR
                 L181)) AND ((L167 OR L168 OR L169 OR L170))
L187         [redacted]
```

1 cite

```
=> d que l200

L188(     13341)SEA FILE=HCAPLUS ABB=ON  PLU=ON  7585-39-9/RN OR .BETA.CYCLODEX
                 TRIN/OBI
L189(      5269)SEA FILE=HCAPLUS ABB=ON  PLU=ON  DRYING APPARATUS+PFT,NT/CT
L190(     24560)SEA FILE=HCAPLUS ABB=ON  PLU=ON  FLUIDIZED BEDS+PFT/CT
L191(     48287)SEA FILE=HCAPLUS ABB=ON  PLU=ON  PARTICLE SIZE+PFT/CT
L192(      9612)SEA FILE=HCAPLUS ABB=ON  PLU=ON  PARTICLE SIZE DISTRIBUTION+PFT
                 /CT
L193(     10093)SEA FILE=HCAPLUS ABB=ON  PLU=ON  COMPRESSION+PFT/CT
L194(      8759)SEA FILE=HCAPLUS ABB=ON  PLU=ON  COMPRESSIBILITY+PFT/CT
L195(        91)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L188 AND (L191 OR L192)
L196(        23)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L188 AND (L193 OR L194)
L197(        64)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L188(L)(GRANUL? OR PELLET?)
L198(      9138)SEA FILE=HCAPLUS ABB=ON  PLU=ON  SIZE REDUCTION+PFT/CT
L199(        34)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L188 AND L198
L200         [redacted]
```

1 cite

```
=> d que l218

L201(     14976)SEA FILE=HCAPLUS ABB=ON  PLU=ON  EVAPORATION+PFT/CT
L202(       423)SEA FILE=HCAPLUS ABB=ON  PLU=ON  DESOLVATION+PFT/CT
L203(     14976)SEA FILE=HCAPLUS ABB=ON  PLU=ON  EVAPORATION+PFT/CT
L204(     31424)SEA FILE=HCAPLUS ABB=ON  PLU=ON  DRYING+PFT,NT/CT
L205(      9466)SEA FILE=HCAPLUS ABB=ON  PLU=ON  WETTING+PFT/CT
L206(      6163)SEA FILE=HCAPLUS ABB=ON  PLU=ON  WETTABILITY+PFT/CT
L207(     21063)SEA FILE=HCAPLUS ABB=ON  PLU=ON  HYDRATION/CT
L208(      2249)SEA FILE=HCAPLUS ABB=ON  PLU=ON  HYDRATES/CT
L209(     48287)SEA FILE=HCAPLUS ABB=ON  PLU=ON  PARTICLE SIZE+PFT/CT
L210(      9612)SEA FILE=HCAPLUS ABB=ON  PLU=ON  PARTICLE SIZE DISTRIBUTION+PFT
                 /CT
L211(     10093)SEA FILE=HCAPLUS ABB=ON  PLU=ON  COMPRESSION+PFT/CT
L212(      8759)SEA FILE=HCAPLUS ABB=ON  PLU=ON  COMPRESSIBILITY+PFT/CT
```

```
L213(      5335)SEA FILE=HCAPLUS ABB=ON  PLU=ON  SOLUBILIZATION/CT
L214(      9138)SEA FILE=HCAPLUS ABB=ON  PLU=ON  SIZE REDUCTION+PFT/CT
L215(       118)SEA FILE=HCAPLUS ABB=ON  PLU=ON  CYCLODEXTRIN(L)(L201 OR L202
                OR L203 OR L204)
L216(       625)SEA FILE=HCAPLUS ABB=ON  PLU=ON  CYCLODEXTRIN(L)((L205 OR L206
                OR L207 OR L208) OR L213)
L217(        30)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L215 AND L216
L218          5 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L217 AND ((L209 OR L210 OR
                L211 OR L212) OR L214)
```

5 cites

```
=> d que l223

L219(     13341)SEA FILE=HCAPLUS ABB=ON  PLU=ON  7585-39-9/RN OR .BETA.CYCLODEX
                TRIN/OBI
L220(       159)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L219(L)PYP/RL
L221(        11)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L220 AND (DRY OR DRYING OR
                DRIED OR EVAPORAT? OR DEHYDRAT?)
L222(         7)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L220 AND (WET OR WETTED OR
                HYDRAT? OR WETTING)
L223          2 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L221 AND L222
```

PYP = physical property

RL = role

2 cites

```
=> s l142 or l165 or l187 or l200 or l218 or l223

L236          8 L142 OR L165 OR L187 OR L200 OR L218 OR L223
```

8 cites for HCAPLUS

```
=> file scisearch

FILE 'SCISEARCH' ENTERED AT 17:40:38 ON 12 MAY 2003
COPYRIGHT 2003 THOMSON ISI

FILE COVERS 1974 TO 9 May 2003 (20030509/ED)

=> d que l89

L83          8626 SEA FILE=SCISEARCH ABB=ON  PLU=ON  .BETA.CYCLODEXTRIN
L85           656 SEA FILE=SCISEARCH ABB=ON  PLU=ON  L83 AND (?PARTICL? OR
                ?SPHER? OR SIZE)
L86           188 SEA FILE=SCISEARCH ABB=ON  PLU=ON  L83 AND (HYDRAT? OR
                REHYDRAT? OR WET OR WETTED OR WETTING OR DISSOLV?(5A)(AQUEOUS
                OR WATER OR H2O))
L88            26 SEA FILE=SCISEARCH ABB=ON  PLU=ON  L86 AND L85
L89             2 SEA FILE=SCISEARCH ABB=ON  PLU=ON  L88 AND ((THERMAL STUDY) OR
                (SIMULATION STUDY))/TI
```

2 cites

```
=> d que l94

L83          8626 SEA FILE=SCISEARCH ABB=ON  PLU=ON  .BETA.CYCLODEXTRIN
L84           320 SEA FILE=SCISEARCH ABB=ON  PLU=ON  L83 AND (EVAP? OR DEHYDRAT?
                OR DRY OR DRIED OR DRYING)
L85           656 SEA FILE=SCISEARCH ABB=ON  PLU=ON  L83 AND (?PARTICL? OR
                ?SPHER? OR SIZE)
L86           188 SEA FILE=SCISEARCH ABB=ON  PLU=ON  L83 AND (HYDRAT? OR
                REHYDRAT? OR WET OR WETTED OR WETTING OR DISSOLV?(5A)(AQUEOUS
                OR WATER OR H2O))
L87            45 SEA FILE=SCISEARCH ABB=ON  PLU=ON  L84 AND L86
L88            26 SEA FILE=SCISEARCH ABB=ON  PLU=ON  L86 AND L85
L90            37 SEA FILE=SCISEARCH ABB=ON  PLU=ON  L87 NOT L88
```

```
L92          22 SEA FILE=SCISEARCH ABB=ON  PLU=ON  L90 AND (PROCESS OR
                PREPAR?)
L93           4 SEA FILE=SCISEARCH ABB=ON  PLU=ON  L92 AND (ENERGETICS OR
                THERMAL OR   MONITORED)/TI
L94           3 SEA FILE=SCISEARCH ABB=ON  PLU=ON  L93 NOT CARVONE

=> d que l97

L83        8626 SEA FILE=SCISEARCH ABB=ON  PLU=ON  .BETA.CYCLODEXTRIN
L84         320 SEA FILE=SCISEARCH ABB=ON  PLU=ON  L83 AND (EVAP? OR DEHYDRAT?
                OR DRY OR DRIED OR DRYING)
L85         656 SEA FILE=SCISEARCH ABB=ON  PLU=ON  L83 AND (?PARTICL? OR
                ?SPHER? OR SIZE)
L86         188 SEA FILE=SCISEARCH ABB=ON  PLU=ON  L83 AND (HYDRAT? OR
                REHYDRAT? OR WET OR WETTED OR WETTING OR DISSOLV?(5A)(AQUEOUS
                OR WATER OR H2O))
L87          45 SEA FILE=SCISEARCH ABB=ON  PLU=ON  L84 AND L86
L88          26 SEA FILE=SCISEARCH ABB=ON  PLU=ON  L86 AND L85
L90          37 SEA FILE=SCISEARCH ABB=ON  PLU=ON  L87 NOT L88
L92          22 SEA FILE=SCISEARCH ABB=ON  PLU=ON  L90 AND (PROCESS OR
                PREPAR?)
L96          15 SEA FILE=SCISEARCH ABB=ON  PLU=ON  L90 NOT L92
L97           3 SEA FILE=SCISEARCH ABB=ON  PLU=ON  L96 AND (BIOMOLECULES OR
                COMPRESSION OR FAST)/TI

=> s l89 or l94 or l97

L237          8 L89 OR L94 OR L97

=> file wpix

FILE 'WPIX' ENTERED AT 17:40:41 ON 12 MAY 2003
COPYRIGHT (C) 2003 THOMSON DERWENT

FILE LAST UPDATED:          5 MAY 2003      <20030505/UP>
MOST RECENT DERWENT UPDATE:     200329        <200329/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> NEW WEEKLY SDI FREQUENCY AVAILABLE --> see NEWS  <<<

>>> SLART (Simultaneous Left and Right Truncation) is now
    available in the /ABEX field. An additional search field
    /BIX is also provided which comprises both /BI and /ABEX <<<

>>> PATENT IMAGES AVAILABLE FOR PRINT AND DISPLAY <<<

>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES,
    SEE http://www.derwent.com/dwpi/updates/dwpicov/index.html <<<

>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE,
    PLEASE VISIT:
 http://www.stn-international.de/training_center/patents/stn_guide.pdf <<<

>>> FOR INFORMATION ON ALL DERWENT WORLD PATENTS INDEX USER
    GUIDES, PLEASE VISIT:
    http://www.derwent.com/userguides/dwpi_guide.html <<<

=> d que l106
```

3 cites

3 cites

8 cites fm Sci search

```
L102(      4883)SEA FILE=WPIX ABB=ON  PLU=ON  CYCLODEXTRIN
L103(       162)SEA FILE=WPIX ABB=ON  PLU=ON  L102(5A) (DRY OR DRYING OR DRIED
                OR EVAPORAT? OR DEHYDRAT?)
L104(        33)SEA FILE=WPIX ABB=ON  PLU=ON  L102(5A)(WET OR WETTED OR
                HYDRAT? OR WETTING)
L105(         3)SEA FILE=WPIX ABB=ON  PLU=ON  L103 AND L104
L106          1 SEA FILE=WPIX ABB=ON  PLU=ON  L105 AND COMPRESS?
```

1 cite

```
=> d que l112

L107(      4883)SEA FILE=WPIX ABB=ON  PLU=ON  CYCLODEXTRIN
L108(       835)SEA FILE=WPIX ABB=ON  PLU=ON  L107(P) (DRY OR DRYING OR DRIED
                OR EVAPORAT? OR DEHYDRAT?)
L109(       644)SEA FILE=WPIX ABB=ON  PLU=ON  L107(P)(WET OR WETTED OR HYDRAT?
                OR WETTING OR DISSOLV?)
L110(       239)SEA FILE=WPIX ABB=ON  PLU=ON  L108 AND L109
L111(        10)SEA FILE=WPIX ABB=ON  PLU=ON  L110 AND COMPRESS?
L112          3 SEA FILE=WPIX ABB=ON  PLU=ON  L111 AND COMPRESS?/TI
```

3 cites

```
=> d que l119

L113(      4883)SEA FILE=WPIX ABB=ON  PLU=ON  CYCLODEXTRIN
L114(       835)SEA FILE=WPIX ABB=ON  PLU=ON  L113(P) (DRY OR DRYING OR DRIED
                OR EVAPORAT? OR DEHYDRAT?)
L115(       644)SEA FILE=WPIX ABB=ON  PLU=ON  L113(P)(WET OR WETTED OR HYDRAT?
                OR WETTING OR DISSOLV?)
L116(       239)SEA FILE=WPIX ABB=ON  PLU=ON  L114 AND L115
L117(        69)SEA FILE=WPIX ABB=ON  PLU=ON  L116 AND (SIZE OR DIAMETER OR
                RADIUS OR ?METER OR ?METRE OR MICRON OR MICRO?)
L118(        12)SEA FILE=WPIX ABB=ON  PLU=ON  L117 AND (AMORPHOUS OR NIMESULIDE
                OR MICROGRANULE OR AGROCHEM? OR CAROTEN? OR SCREENS OR
                UNCOMPLEXED OR ENTERIC OR COMPRESSIBLE OR DUSTING)/TI
L119          10 SEA FILE=WPIX ABB=ON  PLU=ON  L118 NOT UNCOMPLEXED/TI
```

10 cites

```
=> s l106 or l112 or l119

L238          10 L106 OR L112 OR L119
```

10 cites for WPIX (Derwent)

```
=> dup rem l4 l233 l234 l53 l235 l236 l237 l238
```

removing duplicate cites

```
FILE 'MEDLINE' ENTERED AT 17:43:07 ON 12 MAY 2003

FILE 'DRUGU' ENTERED AT 17:43:07 ON 12 MAY 2003
COPYRIGHT (C) 2003 THOMSON DERWENT

FILE 'BIOSIS' ENTERED AT 17:43:07 ON 12 MAY 2003
COPYRIGHT (C) 2003 BIOLOGICAL ABSTRACTS INC.(R)

FILE 'BIOTECHNO' ENTERED AT 17:43:07 ON 12 MAY 2003
COPYRIGHT (C) 2003 Elsevier Science B.V., Amsterdam. All rights reserved.

FILE 'USPATFULL' ENTERED AT 17:43:07 ON 12 MAY 2003
CA INDEXING COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'HCAPLUS' ENTERED AT 17:43:07 ON 12 MAY 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
```

FILE 'SCISEARCH' ENTERED AT 17:43:07 ON 12 MAY 2003

FILE 'WPIX' ENTERED AT 17:43:07 ON 12 MAY 2003

PROCESSING COMPLETED FOR L4
PROCESSING COMPLETED FOR L233
PROCESSING COMPLETED FOR L234
PROCESSING COMPLETED FOR L53
PROCESSING COMPLETED FOR L235
PROCESSING COMPLETED FOR L236
PROCESSING COMPLETED FOR L237
PROCESSING COMPLETED FOR L238
L239 52 DUP REM L4 L233 L234 L53 L235 L236 L237 L238 (8 DUPLICATES REMOVED) 52 cites total
ANSWERS '1-12' FROM FILE MEDLINE
ANSWERS '13-17' FROM FILE DRUGU
ANSWERS '18-30' FROM FILE BIOSIS
ANSWERS '31-32' FROM FILE USPATFULL
ANSWERS '33-38' FROM FILE HCAPLUS
ANSWERS '39-43' FROM FILE SCISEARCH
ANSWERS '44-52' FROM FILE WPIX

=> d ibib ab 1-12

L239 ANSWER 1 OF 52 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2002027622 MEDLINE
DOCUMENT NUMBER: 21377400 PubMed ID: 11485172
TITLE: Enhancement of ibuprofen dissolution via **wet** granulation with beta-cyclodextrin.
AUTHOR: Ghorab M K; Adeyeye M C
CORPORATE SOURCE: Graduate School of Pharmaceutical Sciences, Duquesne University, Pittsburgh, PA 15282, USA.
SOURCE: PHARMACEUTICAL DEVELOPMENT AND TECHNOLOGY, (2001 Aug) 6 (3) 305-14.
Journal code: 9610932. ISSN: 1083-7450.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200201
ENTRY DATE: Entered STN: 20020121
Last Updated on STN: 20020125
Entered Medline: 20020122

AB The purpose was to investigate the effect of **wet** granulation with beta-cyclodextrin (betaCD) on the enhancement of ibuprofen (IBU) dissolution. The effect of the granulation variables on the physical properties as well as the dissolution of tablets prepared from these granules was also examined. Granulation was performed using three granulating solvents: water, ethanol (95 vol%), and isopropanol. Granules were either oven-**dried** for 2 h or air-**dried** for 3 days. The granules or respective physical mixtures were compressed into tablets. Powder X-ray diffraction showed that oven-**dried** granulation resulted in less amorphous entities thatfacilitated IBU-betaCD complexation in solution and enhanced the dissolution of the corresponding tablets compared to the physical mixture with or without oven **drying**. In contrast, air-**dried** granulation did not cause any differences in the X-ray diffraction pattern (crystallinity) or the dissolution compared to the physical mixture without **drying**.

Isopropanol and water, as granulating solvents, enhanced the dissolution of the oven-**dried** batches more than ethanol. The Differential scanning calorimetry (DSC) and Thermogravimetric analysis (TGA) data showed that tablets prepared from oven-**dried** granules, but not air-**dried** granules, had lower AH values and percent loss in weight, respectively, than those prepared from the physical mixture as a result of the expulsion of the water molecules from the betaCD cavity and enhancement of the complexation in solution. These results showed that oven-**dried** granulation of IBU and betaCD provided faster IBU dissolution than the physical mixture; air-**dried** granulation did not substantially affect the dissolution of IBU.

L239 ANSWER 2 OF 52 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 1999434352 MEDLINE
DOCUMENT NUMBER: 99434352 PubMed ID: 10502630
TITLE: Poly(acrylic acid) microspheres containing beta-cyclodextrin: loading and in vitro release of two dyes.
AUTHOR: Bibby D C; Davies N M; Tucker I G
CORPORATE SOURCE: Formulation and Drug Delivery Group, School of Pharmacy, University of Otago, P.O. Box 913, Dunedin, New Zealand.
SOURCE: INTERNATIONAL JOURNAL OF PHARMACEUTICS, (1999 Oct 5) 187 (2) 243-50.
Journal code: 7804127. ISSN: 0378-5173.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199911
ENTRY DATE: Entered STN: 20000111
Last Updated on STN: 20000111
Entered Medline: 19991117

AB Microspheres containing poly(acrylic acid) and beta-cyclodextrin or maltose were prepared by a w/o solvent **evaporation** technique. The dispersed aqueous phase contained poly(acrylic acid) (800 mg) and beta-cyclodextrin or maltose (0, 200 or 800 mg). Food-grade olive oil was the continuous phase. Microsphere particle size was consistently between 15 and 25 microm, and carbohydrate content was in good agreement with that added to the dispersed phase in all cases. Two dyes, phenolphthalein and rhodamine B, having different solubility characteristics and strengths of association with beta-cyclodextrin, were selected for loading and in vitro release studies. Microspheres were loaded by soaking in a saturated propan-2-ol solution of the appropriate dye (6 h). Microsphere dye content ranged between 2.8 and 4.8 mg/g microspheres for phenolphthalein and between 2.2 and 3.7 mg/g for rhodamine B. Release studies were performed in phosphate buffer (pH 7.4; 37 degrees C). No difference in the release profile of either dye was observed between microspheres. The failure of microspheres containing beta-cyclodextrin in particular, to alter the in vitro release kinetics of either dye may be due to a number of factors and include: (i) limited cross-linking giving rise to a the rapid **hydration** of the polymer matrix; (ii) perturbation of the dye-beta-cyclodextrin complex by oil and/or organic solvent residues; and (iii) conformational changes/steric hindrance of the beta-cyclodextrin cavity (due to its covalent binding with PAA) resulting in a reduction in its ability to form inclusion complexes.

L239 ANSWER 3 OF 52 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 93075195 MEDLINE
DOCUMENT NUMBER: 93075195 PubMed ID: 1445343
TITLE: Crystalline beta-cyclodextrin.12H2O reversibly

dehydrates to beta-cyclodextrin.10.5 H2O under ambient conditions.
AUTHOR: Steiner T; Koellner G; Ali S; Zakim D; Saenger W
CORPORATE SOURCE: Institut fur Kristallographie, Freie Universitat Berlin, Germany.
CONTRACT NUMBER: T32 DK07142 (NIDDK)
SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1992 Nov 16) 188 (3) 1060-6.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199212
ENTRY DATE: Entered STN: 19930122
Last Updated on STN: 19990129
Entered Medline: 19921222

AB In contact with mother liquor, crystalline beta-cyclodextrin (beta-CD) **hydrate** has composition approximately beta-CD.12H2O. If crystals are **dried** at ambient conditions (18 degrees C, approximately 50% humidity), the unit cell volume diminishes approximately 30 to 50 A3. X-ray structure analysis of a **dry** crystal (0.89 A resolution, 4617 data, R = 0.059) showed the composition beta-CD.10.5 H2O, with approximately 5.5 water molecules in the beta-CD cavity (7 partially and 2 fully occupied sites) and approximately 5.0 between the beta-CD molecules. The positions of the beta-CD host and of most of the **hydration** waters are conserved during **dehydration**, but the occupancies of the waters in the beta-CD cavity diminish. **Dry** crystals put into solvent re-**hydrate** to the original form. The mechanism of de- and re-**hydration** is not evident.

L239 ANSWER 4 OF 52 MEDLINE
ACCESSION NUMBER: 2002341869 MEDLINE
DOCUMENT NUMBER: 22079455 PubMed ID: 12084504
TITLE: Improved dissolution behaviour of steam-granulated piroxicam.
COMMENT: Erratum in: Eur J Pharm Biopharm 2002 Nov;54(3):361
Erratum in: Abertini Beatrice [corrected to Albertini Beatrice]
AUTHOR: Cavallari Cristina; Albertini Beatrice; Gonzalez-Rodriguez Marisa L; Rodriguez Lorenzo; Abertini Beatrice
CORPORATE SOURCE: Dipartimento di Scienze Farmaceutiche, Universita di Bologna, Bologna, Italy.. cavallar@biocfarm.unibo.it
SOURCE: EUROPEAN JOURNAL OF PHARMACEUTICS AND BIOPHARMACEUTICS, (2002 Jul) 54 (1) 65-73.
Journal code: 9109778. ISSN: 0939-6411.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200212
ENTRY DATE: Entered STN: 20020627
Last Updated on STN: 20030108
Entered Medline: 20021226

AB In this paper we prepared and characterized improved release granulates containing Piroxicam and beta-cyclodextrins (1:2.5 molar ratio), obtained by steam-aided granulation, using a one-step rotogranulator, Rotolab. These granulates were compared to those prepared by traditional **wet** granulation, to the physical mixture, and to the kneaded and **dry** granulates. The experimental data showed a significant

reduction of the water amount required (50%) and of the working time, with respect to traditional **wet** granulation. The samples examined by scanning electron microscopy and fractal analysis revealed morphological differences related to the method of preparation: the steam-granulated material showed a diffuse porosity, as confirmed by the porosity test. Differential scanning calorimetry, infrared and X-ray analysis revealed the absence of polymorphs in the solid state of the drug. The results of the dissolution tests suggest that the steam-aided granulation may be considered a useful method to improve the in vitro dissolution rate of Piroxicam, enabling also a considerable reduction in the processing time.

L239 ANSWER 5 OF 52 MEDLINE
ACCESSION NUMBER: 2002027623 MEDLINE
DOCUMENT NUMBER: 21377401 PubMed ID: 11485173
TITLE: Elucidation of solution state complexation in **wet** -granulated oven-**dried** ibuprofen and beta-cyclodextrin: FT-IR and 1H-NMR studies.
AUTHOR: Ghorab M K; Adeyeye M C
CORPORATE SOURCE: Graduate School of Pharmaceutical Sciences, Duquesne University, Pittsburgh, PA 15282, USA.
SOURCE: PHARMACEUTICAL DEVELOPMENT AND TECHNOLOGY, (2001 Aug) 6 (3) 315-24.
Journal code: 9610932. ISSN: 1083-7450.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200201
ENTRY DATE: Entered STN: 20020121
Last Updated on STN: 20020125
Entered Medline: 20020122

AB The effect of oven-**dried** **wet** granulation on the complexation of beta-cyclodextrin with ibuprofen (IBU) in solution was investigated using Fourier transform infrared spectroscopy (FT-IR), proton nuclear magnetic resonance (1H NMR), and molecular modeling. Granulation was carried out using 5 mL of three different granulating solvents; water, ethanol (95% v/v), and isopropanol and the granules were oven-**dried** at 60 degrees C for 2 h. The granules were compared to oven-**dried** physical mixture and conventionally prepared complex. Phase solubility study was performed to investigate the stability of the granulation-formed complexes in solution. FT-IR was used to examine the complexation in the granules while 1H NMR, and molecular modeling studies were carried out to determine the mechanism of complexation in the water-prepared granules. The solubility studies suggested a 1:1 complex between IBU and betaCD. It also showed that the stability of the complex in solution was in the following order with respect to the granulating solvents: ethanol > water > isopropanol. The FT-IR study revealed a shift in the carboxylic acid stretching band and decrease in the intensities of the C-H bending bands of the isopropyl group and the out-of-plane aromatic ring, of IBU, in granules compared to the oven-**dried** physical mixture. This indicated that granules might have some extent of solid state complexation that could further enhance dissolution and the IBU-betaCD solution state complexation. 1H NMR showed that water prepared oven-**dried** granules had a different 1H NMR spectrum compared to similarly made oven-**dried** physical mixture, indicative of complexation in the former. The 1H NMR and the molecular modeling studies together revealed that solution state complexation from the granules occurred by inclusion of the isopropyl group together with part of the aromatic ring of IBU into the betaCD cavity probably through its wider side. These results indicate that granulation process induced faster

complexation in solution which enhances the solubility and the dissolution rate of poorly soluble drugs. The extent of complexation in the granules was dependent on the type of solvent used.

L239 ANSWER 6 OF 52 MEDLINE
ACCESSION NUMBER: 2001311793 MEDLINE
DOCUMENT NUMBER: 21278537 PubMed ID: 11384851
TITLE: Liposomes encapsulating prednisolone and prednisolone-cyclodextrin complexes: comparison of membrane integrity and drug release.
AUTHOR: Fatouros D G; Hatzidimitriou K; Antimisiaris S G
CORPORATE SOURCE: University of Patras, School of Health Sciences, Laboratory of Pharmaceutical Technology, Department of Pharmacy, 26500 Patras, Greece.
SOURCE: EUROPEAN JOURNAL OF PHARMACEUTICAL SCIENCES, (2001 Jun) 13 (3) 287-96.
Journal code: 9317982. ISSN: 0928-0987.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200109
ENTRY DATE: Entered STN: 20010924
Last Updated on STN: 20010924
Entered Medline: 20010920

AB Inclusion complexes of prednisolone (PR) with beta-cyclodextrin (beta-CD) and hydropropyl-beta-cyclodextrin (HPbeta-CD) were formed by the solvation method, and were characterized by DSC, X-ray diffractometry and FT-IR spectroscopy. PC liposomes incorporating PR as plain drug or inclusion complex were prepared using the **dehydration-rehydration** method and drug entrapment as well as drug release were estimated for all liposome types prepared. The highest PR entrapment value (80% of the starting material) was achieved for PC/Chol liposomes when the HPbeta-CD-PR (2:1, mol/mol) complex was entrapped. The leakage of vesicle encapsulated 5,6-carboxyfluorescein (CF) was used as a measure of the vesicle membrane integrity. As judged from our experimental results liposomes which encapsulate beta-CD-PR complexes are significantly less stable (when their membrane integrity is considered) compared to liposomes of identical lipid compositions which incorporate plain drug or even (in some cases) non-drug incorporating liposomes, which were prepared and studied for comparison. Interestingly, liposomes which encapsulate HPbeta-CD-PR complexes, have very low initial CF latency values, indicating that the leakage of CF is a process of very high initial velocity. Interactions between lipid and cyclodextrin molecules may be possibly resulting in rapid reorganization of the lipid membrane with simultaneous fast release of CF molecules. The release of PR from liposomes was highest when the drug was entrapped in the form of a complex with beta-CD. Nevertheless, the very high entrapment ability of PR in the form of HPbeta-CD-PR complexes in comparison to plain drug is a indubitable advantage of this approach.

L239 ANSWER 7 OF 52 MEDLINE
ACCESSION NUMBER: 2001129995 MEDLINE
DOCUMENT NUMBER: 21023859 PubMed ID: 11147128
TITLE: Liposomes containing drug and cyclodextrin prepared by the one-step spray-**drying** method.
AUTHOR: Skalko-Basnet N; Pavelic Z; Becirevic-Lacan M
CORPORATE SOURCE: Department of Pharmaceutics, Faculty of Pharmacy and Biochemistry, University of Zagreb, A. Kovacica 1, Zagreb, Croatia.. natasab61@hotmail.com

SOURCE: DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, (2000 Dec) 26 (12) 1279-84.
Journal code: 7802620. ISSN: 0363-9045.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010301

AB The one-step spray-**drying** method was applied in the preparation of liposomes containing drug and cyclodextrin (CD). Spray-**dried** lecithin liposomes, entrapping metronidazole or verapamil alone or together with hydroxypropyl-beta-cyclodextrin (HP beta CD), were characterized for morphology, size distribution, and drug entrapment efficiency. The main factor influencing the liposomal size was the volume of aqueous medium used for **hydration** of the spray-**dried** product. No differences in size or entrapment between liposomes prepared by immediate **hydration** of **dried** powder or by **hydration** after 1 year of powder storage at 4 degrees C were observed. All liposomes were tested for their serum stability. The most stable liposomes (still retaining about 10% of the originally entrapped drug even after 24 hr incubation with serum) were liposomes prepared by the direct spray-**drying** of the mixture of lipid, drug, and HP beta CD.

L239 ANSWER 8 OF 52 MEDLINE
ACCESSION NUMBER: 2000443133 MEDLINE
DOCUMENT NUMBER: 20445319 PubMed ID: 10993223
TITLE: Inclusion complex of 3,9-bis(N,N-dimethylcarbamoyloxy)-5H-benzofuro[3,2-c]quinoline-6-one (KCA-098) with heptakis(2,6-di-O-methyl)-beta-cyclodextrin: interaction and dissolution properties.
AUTHOR: Yamada T; Imai T; Ouchi K; Otagiri M; Hirayama F; Uekama K
CORPORATE SOURCE: Pharmaceutical Laboratories, Kissei Pharmaceutical Co., Ltd., Minamiazumi, Nagano, Japan..
tatsuhiko_yamada@pharm.kissei.co.jp
SOURCE: CHEMICAL AND PHARMACEUTICAL BULLETIN, (2000 Sep) 48 (9) 1264-9.
Journal code: 0377775. ISSN: 0009-2363.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200102
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010202

AB Interactions of KCA-098 with heptakis(2,6-di-O-methyl)-beta-cyclodextrin (DM-beta-CyD) in solution and in the solid state were studied by the solubility method, UV and fluorescence spectroscopy, powder X-ray diffractometry, and thermal analysis. The KCA-098/DM-beta-CyD system showed an A(L) type solubility diagram with stability constants of 5870 and 2220 M(-1) in aqueous and 10% methanol solutions, respectively. Following the addition of DM-beta-CyD, the maximum UV wavelength of KCA-098 was shifted to a longer wavelength and the fluorescence intensity was decreased. A similar spectral change was observed when KCA-098 was dissolved in less polar solvents, especially in proton-acceptor solvents, such as acetone and dimethylsulfoxide, suggesting that KCA-098 interacts

with DM-beta-CyD through not only a hydrophobic interaction but also hydrogen bonding. The solid complex of KCA-098 with DM-beta-CyD in a molar ratio of 1:1 was prepared by the kneading method and the solvent **evaporation** method, using organic solvents. Powder X-ray diffractometric and differential scanning calorimetric studies indicated that KCA-098 was dispersed as microparticles on the DM-beta-CyD complex in the solid state prepared by the solvent **evaporation** method although it dispersed as crystals in the sample prepared by the kneading method. The dissolution of KCA-098 from the solid complex prepared by the former method was markedly faster than that prepared by the latter method, although it slowed down with the passage of time. The reduced dissolution of KCA-098 was explained by crystallization to the **hydrate** form in the medium. These data indicate that poorly water-soluble KCA-098 interacts with DM-beta-CyD in water and in the solid state and that a fast-dissolving form of KCA-098 can be obtained by **evaporating** with DM-beta-CyD using organic solvents.

L239 ANSWER 9 OF 52 MEDLINE
ACCESSION NUMBER: 1998339955 MEDLINE
DOCUMENT NUMBER: 98339955 PubMed ID: 9675355
TITLE: Solid state NMR spectroscopy study of molecular motion in cyclomaltoheptaose (beta-cyclodextrin) crosslinked with epichlorohydrin.
AUTHOR: Crini G; Cosentino C; Bertini S; Naggi A; Torri G; Vecchi C; Janus L; Morcellet M
CORPORATE SOURCE: Istituo Scientifico di Chimica e Biochimica G. Ronzoni, Milan, Italy.. gregorio.crini@univ-fcomte.fr
SOURCE: CARBOHYDRATE RESEARCH, (1998 Mar) 308 (1-2) 37-45. Journal code: 0043535. ISSN: 0008-6215.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199807
ENTRY DATE: Entered STN: 19980811
Last Updated on STN: 19980811
Entered Medline: 19980728

AB **Dry** and **hydrated** insoluble cyclomaltoheptaose (beta-cyclodextrin, beta-CD) polymers have been investigated by solid state 13C NMR spectroscopy techniques such as cross polarization/magic angle spinning with dipolar decoupling (CP/MAS), magic angle spinning both with (DD-MAS) and without (MAS) dipolar decoupling and CP/MAS dipolar dephasing (dd-CP/MAS) to allow the assignment of the main 13C signals. In the solid state, the presence of water in the samples resulted in a better resolution reflecting increased mobility. Two distinct components (crosslinked beta-CD and polymerized epichlorohydrin) have been found. The molecular mobility of these two components has been analyzed in terms of relaxation parameters such as 13C spin lattice relaxation (T1) and 1H spin lattice relaxation in the rotating frame (T1 rho). The T1 values of the polymers show that the beta-CD trapped inside the polymers does not seem to undergo changes in its mobility whatever the amount of epichlorohydrin. The addition of water to beta-CD significantly increases the T1 values reflecting strong interaction between beta-CD and the solvent. The T1P values obtained reflect the homogeneous nature of the materials.

L239 ANSWER 10 OF 52 MEDLINE
ACCESSION NUMBER: 96274360 MEDLINE
DOCUMENT NUMBER: 96274360 PubMed ID: 8999433
TITLE: Design and in vivo testing of 17 beta-estradiol-HP beta CD

sublingual tablets.
AUTHOR: Fridriksdottir H; Loftsson T; Gudmundsson J A; Bjarnason G J; Kjeld M; Thorsteinsson T
CORPORATE SOURCE: Department of Pharmacy, University of Iceland, Reykjavik.
SOURCE: PHARMAZIE, (1996 Jan) 51 (1) 39-42.
Journal code: 9800766. ISSN: 0031-7144.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199701
ENTRY DATE: Entered STN: 19970219
Last Updated on STN: 19990129
Entered Medline: 19970123

AB 17 beta-Estradiol is almost insoluble in water. The effect of various cyclodextrins and two different polymers, polyvinylpyrrolidone (PVP) and carboxymethylcellulose (CMC), on the aqueous solubility of 17 beta-estradiol was investigated. 17 beta-Estradiol was **dissolved** in **aqueous** 50% w/v 2-hydroxypropyl-beta- cyclodextrin (HP beta CD) solution containing 0.25% (w/v) CMC and the **dry** 17 beta-estradiol-HP beta CD complex formed by lyophilisation of the solution. Sublingual tablets from the **dry** complex were produced by direct compression. The dissolution of 17 beta-estradiol from tablets containing the drug in a lyophilised HP beta CD complex was determined. For reference the dissolution of 17 beta-estradiol was determined from tablets containing physical mixture of 17 beta-estradiol and HP beta CD or tablets containing 17 beta-estradiol without HP beta CD. Sublingual tablets containing 17 beta-estradiol-HP beta CD in the lyophilised complex demonstrated the fastest dissolution profile and those tablets were selected for further studies in humans. Six postmenopausal women received a sublingual tablet containing 17 beta-estradiol-HP beta CD complex equivalent to 100 micrograms 17 beta-estradiol. Blood samples were collected over a 12 h period and the 17 beta-estradiol plasma concentration was determined. 17 beta-Estradiol was rapidly absorbed from the sublingual tablets, resulting in a peak 17 beta-estradiol plasma concentration of 568 +/- 97 pmol/l 15 min after administration of the tablets, followed by a biphasic elimination.

L239 ANSWER 11 OF 52 MEDLINE
ACCESSION NUMBER: 95219341 MEDLINE
DOCUMENT NUMBER: 95219341 PubMed ID: 7704490
TITLE: Entrapment of cyclodextrin-drug complexes into liposomes: potential advantages in drug delivery.
AUTHOR: McCormack B; Gregoriadis G
CORPORATE SOURCE: Centre for Drug Delivery Research, School of Pharmacy, University of London, U.K.
SOURCE: JOURNAL OF DRUG TARGETING, (1994) 2 (5) 449-54. Ref: 29
Journal code: 9312476. ISSN: 1061-186X.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199505
ENTRY DATE: Entered STN: 19950518
Last Updated on STN: 19980206
Entered Medline: 19950511

AB A novel concept in drug delivery discussed here, takes advantage of

certain properties of the drug "containers" cyclodextrins and liposomes to combine them into a single system thus circumventing problems associated with both systems. The concept, entailing entrapment of water-soluble cyclodextrin-drug inclusion complexes in liposomes, would allow accommodation of insoluble drugs in the aqueous phase of vesicles. This would potentially increase the drug to lipid mass ratio to levels above those attained by conventional drug incorporation into the lipid phase, enlarge the range of insoluble drugs amenable to encapsulation to include, for instance, membrane destabilizing agents, allow targeting of complexes to specific sites and reduce toxicity. In the present work, soluble inclusion complexes of hydroxypropyl-beta-cyclodextrin with dehydroepiandrosterone, retinol and retinoic acid were prepared and entrapped into multilamellar liposomes by the **dehydration-rehydration** procedure. Complex-containing liposomes were then exposed to blood plasma. Results show that complex entrapment into liposomes depends on the lipid composition used. Nearly all of the cyclodextrin and considerable portions of the drugs were found to remain associated with the carrier in the presence of plasma.

L239 ANSWER 12 OF 52 MEDLINE
ACCESSION NUMBER: 92189750 MEDLINE
DOCUMENT NUMBER: 92189750 PubMed ID: 1799430
TITLE: [Evaluation of beta-cyclodextrins as formulated coadjuvants for improved drug solubility].
Valutazione delle beta-ciclodestrine quali coadiuvanti formulativi per farmaci poco solubili.
AUTHOR: Rosso F; Maffione G
CORPORATE SOURCE: aleas s.p.a., Milano.
SOURCE: BOLLETTINO CHIMICO FARMACEUTICO, (1991 Oct) 130 (9) 355-71.
Journal code: 0372534. ISSN: 0006-6648.
PUB. COUNTRY: Italy
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Italian
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199204
ENTRY DATE: Entered STN: 19920509
Last Updated on STN: 19990129
Entered Medline: 19920421

AB Cyclodextrins are known to form inclusion complexes in acqueous solutions with various types of organic substance, also a lot of hydrophobic drugs. Drugs/beta CD complexes obtained applying different techniques, eventually in solid state, usually show an improvement of solubility or at last in dissolution characteristics. In the present work, drug-bCD system or interacted products are prepared in order to screen different method of preparation in respect to the bioavailability increase (evaluated in vitro) and to the feasibility of the manufacturing process. From the galenical development point of view the beta CD/drug system prepared in different molar ratios were characterized by their physico-chemical properties (melting point, thermal behaviour by DSC, moisture content, IR spectrum, UV spectrum, equilibrium solubility, dissolution kinetics). The applied methods of preparation are well known industrial process as **dry** mixing (simple physical mixture), co-milling, kneading, coprecipitation, freeze **drying**, **wet** granulation methods. From the obtained in vitro results, it would seem that solubility and dissolution characteristics are improved by the drug-beta CD interaction, applying very common simply economic methods so the choice of the preferred manufacturing method will be delayed depending on in vivo performance and clinical needs and long term stability studies.

=> d ibib ab 13-17

L239 ANSWER 13 OF 52 DRUGU COPYRIGHT 2003 THOMSON DERWENTDUPLICATE 5
ACCESSION NUMBER: 1999-24977 DRUGU G
TITLE: **Optimization** of the process of direct pelleting of a mixture of **beta-cyclodextrin**/ microcrystalline cellulose in a fluid **bed** rotary granulator.
AUTHOR: Palugan L; Cerea M; Vecchio C; Zema L; Sangalli M E; Maroni A; Giordano F; Gazzaniga A
CORPORATE SOURCE: Univ.Milan; Univ.Parma
LOCATION: Milan; Parma, It.
SOURCE: Boll.Chim.Farm. (138, No. 3, 79-85, 1999) 6 Fig. 3 Tab. 4 Ref.
CODEN: BCFAAI ISSN: 0006-6648
AVAIL. OF DOC.: Istituto Chimico Farmaceutico, Universita di Milano, Milano. Italy.
LANGUAGE: Italian
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB A method for direct pelleting in a fluid **bed** rotary granulator (Glatt GPCG 1.1) was evaluated in comparison with extrusion/ spheronization technology for preparation of pellets from a mixture of microcrystalline cellulose (MCC, Avicel PH101, FMC) and **beta-cyclodextrin** (beta-CD, Kleptose, Roquette). The pellets were characterized by mean diameter (granulometry), friability and elongation ratio (maximum/minimum diameter ratio). Multiple regression analyses using wall charts were performed to display the effects of changes in independent variables in terms of the pellet parameters. This study provided a preliminary screening phase that was limited but necessary in obtaining a more extensive project for the statistical optimization of the process sequence.

L239 ANSWER 14 OF 52 DRUGU COPYRIGHT 2003 THOMSON DERWENTDUPLICATE 6
ACCESSION NUMBER: 1995-45627 DRUGU G
TITLE: Characterization of **beta-cyclodextrin** for direct compression tableting: II. The role of moisture in the **compactibility** of **beta-cyclodextrin**.
AUTHOR: Pande G S; Shangraw R F
CORPORATE SOURCE: Glaxo; Univ.Maryland
LOCATION: Research Triangle Park, N.C.; Baltimore, Md., USA
SOURCE: Int.J.Pharm. (124, No. 2, 231-39, 1995) 5 Fig. 3 Tab. 16 Ref.
CODEN: IJPHDE ISSN: 0378-5173
AVAIL. OF DOC.: Department of Pharmaceutics, School of Pharmacy, University of Maryland, Baltimore, MD 21201, U.S.A. (R.F.S.).
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB The effect of moisture on the compactibility of a modified **beta-cyclodextrin** (BCD-DC, Roquette) and a commercial **beta-cyclodextrin** (Kleptose, Roquette) was examined. The moisture sorption and desorption isotherms displayed considerable hysteresis. Crystal **hydrates** of BCD-DC and Kleptose contained 11 moles of water per mole of **beta-cyclodextrin**. The surface area of both samples varied significantly with varying pretreatment conditions. For both BCD-DC and Kleptose samples, compactibility was lost on removal of water. A moisture content of about 14% appeared to be

optimum for maximum compactibility of both samples.

L239 ANSWER 15 OF 52 DRUGU COPYRIGHT 2003 THOMSON DERWENT
ACCESSION NUMBER: 1994-38396 DRUGU G
TITLE: Use of **dehydrated beta-cyclodextrin** as pharmaceutical excipient.
AUTHOR: Martini A; Torricelli C; Muggeti L; De Ponti R
CORPORATE SOURCE: Farmitalia-Erba
LOCATION: Milan, Italy
SOURCE: Drug Dev.Ind.Pharm. (20, No. 15, 2381-93, 1994) 6 Fig. 3 Tab. 17 Ref.
CODEN: DDIPD8 ISSN: 0363-9045
AVAIL. OF DOC.: Farmitalia Carlo Erba srl; R & D-Pharmaceutical Development, via Papa Giovanni XXIII, 23, 20014 Nerviano (Milano), Italy.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB The in-vitro dissolution rates of temazepam (TE), FCE-24578, FCE-24304 (exemestane) and griseofulvin (all Farmitalia-Erba) were increased more by forming intimate physical mixtures with **dehydrated** than **hydrated beta-cyclodextrin** (BCD, Spad-Roquette). Wettability, aqueous affinity and water penetration rates of anhydrous BCD were greater than for **hydrated** BCD. Although not forming inclusion complexes in the solid state, anhydrous BCD increases the rate of complex formation in solution with a strong influence on dissolution of sparingly-soluble drugs.

L239 ANSWER 16 OF 52 DRUGU COPYRIGHT 2003 THOMSON DERWENT
ACCESSION NUMBER: 1993-00237 DRUGU G
TITLE: Characterization of the Tableting Properties of **beta-Cyclodextrin** and the Effects of Processing Variables on Inclusion Complex Formation, **Compactibility** and Dissolution.
AUTHOR: Shangraw R F; Pande G S; Gala P
CORPORATE SOURCE: Warner-Parke-Davis
LOCATION: Baltimore, Maryland, Morris Plains, New Jersey, United States
SOURCE: Drug Dev.Ind.Pharm. (18, No. 17, 1831-51, 1992) 13 Fig. 1 Tab. 23 Ref.
CODEN: DDIPD8 ISSN: 0363-9045
AVAIL. OF DOC.: University of Maryland, School of Pharmacy, 20 N. Pine Street, Baltimore, MD 21201, U.S.A.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB **Beta-cyclodextrins** (CY, UR Industry Inc., Kleptose, Roquette Corp., B. Celdrex, Nihon Shokohin, Kako Co., and Amaizo, American Maize Products Co.) had poor flow but excellent compactibility superior to spray **dried** lactose (LA, Hydrous lactose NF, Fast Flow, Foremost Whey Products) and dicalcium phosphate dihydrate (DI, Ditab, Stauffer Chemical Co.) but inferior to micro-crystalline cellulose (CE, Avicel-PH102, FMC Corp.). CY formed an inclusion complex with progesterone (PR, Paddock Lab Inc.) in tablets formulated with sodium croscarmellose (Ac-Di-Sol, FMC Corp.), colloidal silica (Ca-O-Sil, Cabot Corporation) and magnesium stearate (MS). Addition of polyvinyl pyrrolidone or alcohol reduced complex formation. PR dissolved faster from CY- than from CE-tablets into water or sodium lauryl sulfate solution.

L239 ANSWER 17 OF 52 DRUGU COPYRIGHT 2003 THOMSON DERWENT
ACCESSION NUMBER: 1990-46653 DRUGU G
TITLE: The Influence of Water Content on the **Binding** Capacity of **beta-Cyclodextrin**.
AUTHOR: Giordano F; Gazzaniga A; Bettinetti G P; Manna A la
LOCATION: Pavia, Milan, Florence, Italy
SOURCE: Int.J.Pharm. (62, No. 2-3, 153-56, 1990) 3 Fig. 12 Ref.
CODEN: IJPHDE ISSN: 0378-5173
AVAIL. OF DOC.: Dipartimento di Chimica Farmaceutica, Universita di Pavia, Viale Taramelli 12, 27100 Pavia, Italy.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB The hardness of tablets prepared from **beta-cyclodextrin** (BCD; Nihon Shokuhin Kako) increased with water content of the material. The tablet hardness at a given water content was greater if anhydrous BCD (ABCD) was allowed to take up water before compressing than if aged BCD containing the same amount of water was used. The hardness of ABCD tablets decreased on storage when **rehydration** occurred. The compression of formulations containing BCD may be critically dependent upon the **drying** process employed as it influences the nature of the water present (bonded or adsorbed).

IDS

=> d ibib ab 18-30

L239 ANSWER 18 OF 52 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 3
ACCESSION NUMBER: 2000:451635 BIOSIS
DOCUMENT NUMBER: PREV200000451635
TITLE: **Hydration** of **beta-cyclodextrin** : A molecular dynamics simulation study.
AUTHOR(S): Winkler, R. G. (1); Fioravanti, S. (1); Ciccotti, G.; Margheritis, C.; Villa, M.
CORPORATE SOURCE: (1) Abteilung Theoretische Physik, Universitaet Ulm, D-89069, Ulm Germany
SOURCE: Journal of Computer-Aided Molecular Design, (October, 2000) Vol. 14, No. 7, pp. 659-667. print.
ISSN: 0920-654X.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB We study by molecular dynamics simulations the **hydration** of **beta-cyclodextrin**. Our simulations show that within these barrel-shaped molecules hydrophobicity dominates, while at the top and bottom sides of the barrel interactions with water are mostly hydrophilic in nature. These results agree with crystallographic data at 120 K and, in particular, with the spontaneous **hydration** process of a cyclodextrin crystal in **wet atmosphere**. The predicted structure of the **hydration** shells is discussed and compared with previous molecular mechanics calculations which report an overall hydrophobic behavior. Moreover, the temperature dependence of the **hydration** process is discussed.

L239 ANSWER 19 OF 52 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 7
ACCESSION NUMBER: 1994:341912 BIOSIS
DOCUMENT NUMBER: PREV199497354912
TITLE: Crystalline **beta-cyclodextrin**

hydrate at various humidities: **Fast**, continuous, and reversible **dehydration** studied by X-ray diffraction.
AUTHOR(S): Steiner, Thomas (1); Koellner, Gertraud
CORPORATE SOURCE: (1) Inst. Kristallographie, Freie Univ. Berlin, Takustrasse 6, D-14195 Berlin Germany
SOURCE: Journal of the American Chemical Society, (1994) Vol. 116, No. 12, pp. 5122-5128.
ISSN: 0002-7863.
DOCUMENT TYPE: Article
LANGUAGE: English

L239 ANSWER 20 OF 52 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2003:13265 BIOSIS
DOCUMENT NUMBER: PREV200300013265
TITLE: Solvent and guest isotope effects on complexation thermodynamics of alpha-, beta-, and 6-amino-6-deoxy-**beta-cyclodextrins**.
AUTHOR(S): Rekharsky, Mikhail V.; Inoue, Yoshihisa (1)
CORPORATE SOURCE: (1) Department of Molecular Chemistry, Osaka University, 2-1 Yamada-oka, Suita, 565-0871, Japan: inoue@chem.eng.osaka-u.ac.jp Japan
SOURCE: Journal of the American Chemical Society, (October 16 2002) Vol. 124, No. 41, pp. 12361-12371. print.
ISSN: 0002-7863.
DOCUMENT TYPE: Article
LANGUAGE: English
AB The stability constant (K), standard free energy (DELTAGdegree), enthalpy (DELTAHdegree), and entropy changes (TDELTASdegree) for the complexation of native alpha- and **beta-cyclodextrins** (CDs) and 6-amino-6-deoxy-beta-CD with more than 30 neutral, positively, and negatively charged guests, including seven fully or partially deuterated guests, have been determined in phosphate buffer solutions (pH/pD 6.9) of hydrogen oxide (H2O) or deuterium oxide (D2O) at 298.15 K by titration microcalorimetry. Upon complexation with these native and modified CDs, both nondeuterated and deuterated guests examined consistently exhibited higher affinities (by 5-20%) in D2O than in H2O. The quantitative affinity enhancement in D2O versus H2O directly correlates with the **size** and strength of the **hydration** shell around the charged/hydrophilic group of the guest. For that reason, negatively/positively charged guests, possessing a relatively large and strong **hydration** shell, afford smaller KH2O/KD2O ratios than those for neutral guests with a smaller and weaker **hydration** shell. Deuterated guests showed lower affinities (by 5-15%) than the relevant nondeuterated guests in both H2O and D2O, which is most likely ascribed to the lower ability of the C-D bond to produce induced dipoles and thus the reduced intracavity van der Waals interactions. The excellent enthalpy-entropy correlation obtained can be taken as evidence for the very limited conformational changes upon transfer of CD complexes from H2O to D2O.

L239 ANSWER 21 OF 52 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2003:102797 BIOSIS
DOCUMENT NUMBER: PREV200300102797
TITLE: Formation of fine drug **particles** by cogrinding with cyclodextrins. I. The use of **beta-cyclodextrin** anhydrate and **hydrate**.
AUTHOR(S): Wongmekiat, Arpansiree; Tozuka, Yuichi; Oguchi, Toshio; Yamamoto, Keiji (1)
CORPORATE SOURCE: (1) Graduate School of Pharmaceutical Sciences, Chiba

University, 1-33 Yayoi-cho, Inage-ku, Chiba, 263-8522, Japan: yamamotk@p.chiba-u.ac.jp Japan
SOURCE: Pharmaceutical Research (Dordrecht), (December 2002, 2002) Vol. 19, No. 12, pp. 1867-1872. print. ISSN: 0724-8741.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Purpose: To improve the micromeritical properties of pranlukast (PRK) **hydrate**, a cogrinding process with cyclodextrin was used, and the formation of fine drug **particles** was investigated. Methods: PRK crystals were ground with either **beta-cyclodextrin** (beta-CD) anhydrate or beta-CD **hydrate** crystals at a mixing molar ratio of 2:1 (beta-CD:PRK) to prepare the ground mixtures (GMs). Powder X-ray diffraction measurement and **particle size** analysis were performed. Results: The two GMs differed from one another in appearance, wettability, and fine **particle** production. Quantitative determination demonstrated that when the beta-CD **hydrate**/PRK GM was dispersed in water, 96% of PRK loaded in GM became fine **particles** smaller than 0.8 mum. In contrast, only 1.4% of PRK in GM transformed to fine **particles** in the case of beta-CD anhydrate/PRK GM. The PRK fine **particles** were considered to be dispersed as small crystals. The stability of PRK **particles** in the aqueous solution was improved by the addition of a water-soluble polymer. Conclusion: Cogrinding with a beta-CD of higher water content can be an effective method to prepare fine drug **particles** at the submicron level.

L239 ANSWER 22 OF 52 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2003:110159 BIOSIS
DOCUMENT NUMBER: PREV200300110159
TITLE: A novel **particle** engineering technology to enhance dissolution of poorly water soluble drugs: Spray-freezing into liquid.
AUTHOR(S): Rogers, True L.; Nelsen, Andrew C.; Hu, Jiahui; Brown, Judith N.; Sarkari, Marazban; Young, Timothy J.; Johnston, Keith P.; Williams, Robert O., III (1)
CORPORATE SOURCE: (1) College of Pharmacy, University of Texas at Austin, (Mailstop A 1920), Austin, TX, 78712-1074, USA: williro@mail.utexas.edu USA
SOURCE: European Journal of Pharmaceutics and Biopharmaceutics, (November 2002, 2002) Vol. 54, No. 3, pp. 271-280. print. ISSN: 0939-6411.
DOCUMENT TYPE: Article
LANGUAGE: English
AB A novel cryogenic spray-freezing into liquid (SFL) process was developed to produce microparticulate powders consisting of an active pharmaceutical ingredient (API) molecularly embedded within a pharmaceutical excipient matrix. In the SFL process, a feed solution containing the API was atomized beneath the surface of a cryogenic liquid such that the liquid-liquid impingement between the feed and cryogenic liquids resulted in intense atomization into microdroplets, which were frozen instantaneously into **microparticles**. The SFL micronized powder was obtained following lyophilization of the frozen **microparticles** . The objective of this study was to develop a **particle** engineering technology to produce micronized powders of the hydrophobic drug, danazol, complexed with hydroxypropyl-**beta-cyclodextrin** (HPbetaCD) and to compare these SFL micronized powders to inclusion complex powders produced from other techniques, such as co-grinding of dry powder mixtures and lyophilization of bulk solutions. Danazol and HPbetaCD were **dissolved** in a

water/tetrahydrofuran cosolvent mixture prior to SFL processing or slow freezing. Identical quantities of the API and HPbetaCD used in the solutions were co-ground in a mortar and pestle and blended to produce a co-ground physical mixture for comparison. The powder samples were characterized by differential scanning calorimetry (DSC), powder X-ray diffraction (XRD), Fourier transform infrared spectrometry (FTIR), scanning electron microscopy, surface area analysis, and dissolution testing. The results provided by DSC, XRD, and FTIR suggested the formation of inclusion complexes by both slow-freezing and SFL. However, the specific surface area was significantly higher for the latter. Dissolution results suggested that equilibration of the danazol/HPbetaCD solution prior to SFL processing was required to produce the most soluble conformation of the resulting inclusion complex following SFL. SFL micronized powders exhibited better dissolution profiles than the slowly frozen aggregate powder. Results indicated that micronized SFL inclusion complex powders **dissolved** faster in **aqueous** dissolution media than inclusion complexes formed by conventional techniques due to higher surface areas and stabilized inclusion complexes obtained by ultra-rapid freezing.

L239 ANSWER 23 OF 52 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:122775 BIOSIS
DOCUMENT NUMBER: PREV200100122775
TITLE: Influence of **wet** granulation and lubrication on the powder and tableting properties of codried product of microcrystalline cellulose with **beta-cyclodextrin**.
AUTHOR(S): Wu, Jen-Sen; Ho, Hsiu-O.; Sheu, Ming-Thau (1)
CORPORATE SOURCE: (1) Graduate Institute of Pharmaceutical Sciences, Taipei Medical College, 250 Wu-Hsing Street, Taipei: mingsheu@tmc.edu.tw Taiwan
SOURCE: European Journal of Pharmaceutics and Biopharmaceutics, (January, 2001) Vol. 51, No. 1, pp. 63-69. print. ISSN: 0939-6411.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The individual influence of **wet** granulation and lubrication on the powder and tableting properties of codried product of microcrystalline cellulose (MCC) with **beta-cyclodextrin** (beta-CD) was examined in this study. Avicel PH 101 and 301 were included for comparison. The codried product, Avicel PH 101 and 301 were granulated with water, and the granules were milled to retain three different **size** fractions: 37-60 mum, 60-150 mum, and 150-420 mum. The original Avicels and codried product were lubricated with magnesium stearate in three different percentages (0.2, 0.5, and 1.0%). The results showed that the powder flowability and disintegration of codried product and Avicels were significantly improved after **wet** granulation. However, the compactibility of codried product and Avicels decreased with increasing **particle size**. Nevertheless, the compactibility of the codried excipient after granulation was still better than the non-granulated Avicel PH 101 and 301. On the other hand, codried product and Avicels were sensitive to lubrication and resulted in decreasing compactibility and increasing disintegration. Because of the rounder shape of **particles**, the codried excipient was more sensitive to magnesium stearate and produced weaker tablets than did Avicels.

L239 ANSWER 24 OF 52 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:59995 BIOSIS

DOCUMENT NUMBER: PREV200100059995
TITLE: Inclusion complex of 3,9-bis(N,N-dimethylcarbamoyloxy)-5H-benzofuro(3,2-c)quinoline-6-one (KCA-098) with heptakis(2,6-di-O-methyl)-**beta-cyclodextrin**: Interaction and dissolution properties.
AUTHOR(S): Yamada, Tatsuhiko (1); Imai, Teruko; Ouchi, Kiyohisa; Otagiri, Masaki; Hirayama, Fumitoshi; Uekama, Kaneto
CORPORATE SOURCE: (1) Pharmaceutical Laboratories, Kissei Pharmaceutical Co., Ltd., 4365-1 Kashiwabara Hotaka, Minamiazumi, Nagano, 399-8304: tatsuhiko_yamada@pharm.kissei.co.jp Japan
SOURCE: Biological & Pharmaceutical Bulletin, (September, 2000) Vol. 23, No. 9, pp. 1264-1269. print.
ISSN: 0918-6158.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Interactions of KCA-098 with heptakis(2,6-di-O-methyl)-**beta-cyclodextrin** (DM-beta-CyD) in solution and in the solid state were studied by the solubility method, UV and fluorescence spectroscopy, powder X-ray diffractometry, and thermal analysis. The KCA-098/DM-beta-CyD system showed an AL type solubility diagram with stability constants of 5870 and 2220 M-1 in aqueous and 10% methanol solutions, respectively. Following the addition of DM-beta-CyD, the maximum UV wavelength of KCA-098 was shifted to a longer wavelength and the fluorescence intensity was decreased. A similar spectral change was observed when KCA-098 was dissolved in less polar solvents, especially in proton-acceptor solvents, such as acetone and dimethylsulfoxide, suggesting that KCA-098 interacts with DM-beta-CyD through not only a hydrophobic interaction but also hydrogen bonding. The solid complex of KCA-098 with DM-beta-CyD in a molar ratio of 1:1 was prepared by the kneading method and the solvent evaporation method, using organic solvents. Powder X-ray diffractometric and differential scanning calorimetric studies indicated that KCA-098 was dispersed as **microparticles** on the DM-beta-CyD complex in the solid state prepared by the solvent evaporation method although it dispersed as crystals in the sample prepared by the kneading method. The dissolution of KCA-098 from the solid complex prepared by the former method was markedly faster than that prepared by the latter method, although it slowed down with the passage of time. The reduced dissolution of KCA-098 was explained by crystallization to the **hydrate** form in the medium. These data indicate that poorly water-soluble KCA-098 interacts with DM-beta-CyD in water and in the solid state and that a fast-dissolving form of KCA-098 can be obtained by evaporating with DM-beta-CyD using organic solvents.

L239 ANSWER 25 OF 52 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:127283 BIOSIS
DOCUMENT NUMBER: PREV200000127283
TITLE: Properties and the inclusion behavior of 6-O-alpha-D-galactosyl- and 6-O-alpha-D-mannosyl-cyclodextrins.
AUTHOR(S): Okada, Yasuyo (1); Matsuda, Kazuha; Hara, Koji; Hamayasu, Kenichi; Hashimoto, Hitoshi; Koizumi, Kyoko
CORPORATE SOURCE: (1) School of Pharmaceutical Sciences, Mukogawa Women's University, 11-68 Koshien Kyuban-cho, Nishinomiya, 663-8179 Japan
SOURCE: Chemical & Pharmaceutical Bulletin (Tokyo), (Nov., 1999) Vol. 47, No. 11, pp. 1564-1568.
ISSN: 0009-2363.
DOCUMENT TYPE: Article

LANGUAGE: English
SUMMARY LANGUAGE: English
AB The novel heterogeneous branched cyclodextrins (CDs), 6-O-alpha-D-galactosyl-alpha, -beta, and -gammaCDs (Gal-alpha, -beta, and -gammaCDs) and 6-O-alpha-D-mannosyl-alpha, -beta, and -gammaCDs (Man-alpha, -beta, and -gammaCDs) **dissolved** sufficiently in **water** and in 10-50% (v/v) methanol aqueous solutions, as did the homogeneous branched CDs, 6-O-alpha-D-glucosyl-alpha, -beta, and -gammaCDs (Glc-alpha, -beta, and -gammaCDs). The solubilities of heterogeneous branched CDs were higher than those of each parent non-branched CDs. The hemolytic activities of heterogeneous and homogeneous branched CDs were lower than those of each parent non-branched CDs and the hemolytic activity became weaker in the order of non-branched CD>Man-CD>Glc-CD>Gal-CD in each series of alpha, beta, and gammaCD. AL type solubility-phase diagrams were displayed in the formation of inclusion complexes of the guest compounds of small **size** (methyl benzoate, estriol, and dexamethasone) with Gal-, Man-, and Glc-CDs, and marked differences among the three kinds of branched CDs could not be detected. However, solubility-phase diagrams between these branched CDs and the insoluble guest compounds of large cyclic structure (cyclosporin A, tacrolimus, and amphotericin B) showed Ap type, and the improvement of water solubilities of these guest compounds with three kinds of branched CDs was enhanced in the order of Man-CDs>Glc-CDs>Gal-CDs.

L239 ANSWER 26 OF 52 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1997:216388 BIOSIS
DOCUMENT NUMBER: PREV199799522892
TITLE: **Particle** and **powder properties** of cyclodextrins.
AUTHOR(S): Munoz-Ruiz, Angel (1); Paronen, Petteri
CORPORATE SOURCE: (1) Dep. Pharmaceutics, Univ. Kuopio, PO Box 1627, Kuopio 70211 Finland
SOURCE: International Journal of Pharmaceutics (Amsterdam), (1997) Vol. 148, No. 1, pp. 33-39.
ISSN: 0378-5173.
DOCUMENT TYPE: Article
LANGUAGE: English
AB The **particle** and powder properties of alpha-, beta-, gamma- and hydroxypropyl-beta- (HP-**beta**) **cyclodextrins** (CDs) were examined. Special attention was paid to water interaction and thermal properties of CDs. The CDs studied showed big differences in **particle size** distribution and **particle** shape.
In all cases, with the exception of beta-CD, the log-normal distribution described adequately the **particle size** distribution.
However, the beta-distribution characterized well **particle** shape factor distribution. The typical alpha and beta parameters obtained from the beta-distribution fitting are related to **sphericity** and shape uniformity of the **particles**. Water content results for CDs, obtained by loss on **drying** at 160 degree C and Karl Fisher methods, yielded similar results; thus, it was possible to **evaporate** practically all the water at 160 degree C. Water content of CDs 'as received' was dependent on the storage history of the samples after manufacturing. The DSC profiles of the CDs showed a broad, intense endothermic effect in the range 20-130 degree C, this asymmetric peak was ascribed to water removal. alpha-CD showed a characteristic peak with an onset temperature 138 degree C. This peak seems to be independent of water content, and only small modifications are observed after **drying** at high temperature. Thus, a feasible structural change is associated with this peak.

L239 ANSWER 27 OF 52 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1992:39799 BIOSIS
DOCUMENT NUMBER: BR42:15949
TITLE: **FLUIDIZED** BED AGGLOMERATION OF **BETA CYCLODEXTRIN.**
AUTHOR(S): PANDE G S; SHANGRAW R F
CORPORATE SOURCE: DEP. PHARMACEUTICS, UNIV. MD., BALTIMORE, MD. 21201.
SOURCE: AAPS (AMERICAN ASSOCIATION OF PHARMACEUTICAL SCIENTISTS) SIXTH ANNUAL MEETING AND EXPOSITION, WASHINGTON, D.C., USA, NOVEMBER 17-21, 1991. PHARM RES (N Y), (1991) 8 (10 SUPPL), S118.
CODEN: PHREEB. ISSN: 0724-8741.
DOCUMENT TYPE: Conference
FILE SEGMENT: BR; OLD
LANGUAGE: English

L239 ANSWER 28 OF 52 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1990:604 BIOSIS
DOCUMENT NUMBER: BA89:604
TITLE: ORIENTATIONAL ORDERING AND DYNAMICS OF THE **HYDRATE** AND EXCHANGEABLE HYDROGEN ATOMS IN CRYSTALLINE CRAMBIN.
AUTHOR(S): USHA M G; WITTEBORT R J
CORPORATE SOURCE: DEP. CHEM., UNIV. LOUISVILLE, LOUISVILLE, KY. 40292.
SOURCE: J MOL BIOL, (1989) 208 (4), 669-678.
CODEN: JMOBAK. ISSN: 0022-2836.
FILE SEGMENT: BA; OLD
LANGUAGE: English

AB Deuterium nuclear magnetic resonance studies of crambin crystals grown from deuterated solvent (2H2O/CH3CH2O2H or H2O/C2H3CH2OH) are reported. The extent to which the **hydrate** and exchangeable hydrogen atoms are dynamically disordered are then determined from the **size** of the residual deuterium quadrupole couplings, .hivin.q.hivin.c.hivin.c. Rapid molecular reorientation (.tau.c-1 > 105 s-1) reduces the magnitude of the quadrupole coupling from its static value (216 kHz for solid water). We find that the room temperature spectrum of crambin is dominated by two features: a sharp line with very small residual quadrupolar coupling less than 3 kHz, and a broad pattern with a quadrupolar coupling in the range 185 to 195 kHz. The former is indicative of very nearly isotropically reorienting deuterons, whereas the latter is somewhat narrower than that observed for the amide deuterons of poly-.gamma.-benzyl-L-glutamate and thus indicative of deuterons that are almost but not completely stationary. By considering the nuclear magnetic resonance spectrum intensities along with the amino acid sequence, X-ray structure and the manner in which quadrupole couplings are reduced by dynamics, we conclude that the nuclear magnetic resonance signal from most of the water molecules of **hydration** are contained in the sharp line, i.e. reorient nearly isotropically in the crystalline protein. Unlike bulk water, which freezes abruptly in the manner of a phase transition, the water of **hydration** in crambin has a broad freezing range from 180 to 250K, as evidenced by the decreasing intensity of the sharp line that disappears at 180K. At temperatures between 150 and 200K, a typical **hydrate** molecule reorients at a rate comparable to the quadrupole coupling. 104 s-1 to 105 s-1, a process that occurs in hexagonal ice in the range of 240 to 270K. At 140K, the **hydrate** is stationary, .tau.c-1 < 103 s-1. Studies of the protein crystallized from solvent deuterated only at the non-exchangeable methyl group of ethanol confirm that ethanol is in the lattice and show that this solvate behaves in much the same way as the **hydrate**. The refined X-ray structure has identified four ethanol solvate molecules. The deuterium spectrum at room temperature has a well-defined residual pattern with

.hivin.q.hivin.c.hivin.c = 2.2 kHz, i.e. a small-order parameter consistent with nearly isotropically reorienting molecules. The spectrum width broadens substantially only at temperatures below 200K and achieves the characteristic spectrum of a rotating methyl group with stationary C-C axis at 140K. The results obtained from crambin are compared with those of hexagonal ice as well as with the **hydrates** of .alpha. and .**beta**.-**cyclodextrin**, all of which show distinct behavior. Relaxation experiments show that the **hydrate** in crambin reorients with a correlation time 40-fold longer than that in bulk water at 287K, and that the amide deuterons undergo librational motions of the amplitude and rate predicted by normal-mode dynamic simulations.

L239 ANSWER 29 OF 52 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1987:445542 BIOSIS
DOCUMENT NUMBER: BA84:101380
TITLE: RED BEET ROOT SPRAY-DRIED AND FREEZE-DRIED EXTRACTS.
AUTHOR(S): LEJEUNE B; POURRAT A; POUGET M-P
CORPORATE SOURCE: LAB. PHARMACIE GALENIQUE PHARMACOTECHNIE, FAC. PHARMACIE, 28 PLACE HENRI DUNANT, 63001 CLERMONT-FERRAND CEDEX.
SOURCE: ANN PHARM FR, (1986 (1987)) 44 (6), 461-466.
CODEN: APFRAD. ISSN: 0003-4509.
FILE SEGMENT: BA; OLD
LANGUAGE: French
AB The realization of spray-dried and freeze-dried red beet root extracts is carried out. Various excipients used to save the coloring matter stability and prevent future **wetting** are tested. Best results are obtained with .**beta**.-**cyclodextrin**. Glycolys D and Aerosil 200. Such products have a uniform **particle size** distribution and a good flowability, which assure facilities for their utilization in dry pharmaceutical forms.

L239 ANSWER 30 OF 52 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1985:400788 BIOSIS
DOCUMENT NUMBER: BA80:70780
TITLE: **CRYSTALLINITY CHANGES** OF ALPHA AND **BETA CYCLODEXTRINS** BY GRINDING.
AUTHOR(S): NAKAI Y; YAMAMOTO K; TERADA K; KAJIYAMA A
CORPORATE SOURCE: FACULTY PHARMACEUTICAL SCI., CHIBA UNIV., 1-33 YAYOICHO CHIBA 260, JAPAN.
SOURCE: YAKUGAKU ZASSHI, (1985) 105 (6), 580-585.
CODEN: YKKZAJ. ISSN: 0372-7750.
FILE SEGMENT: BA; OLD
LANGUAGE: Japanese
AB The crystallinity of cyclodextrins was evaluated by using powder X-ray diffraction techniques. .alpha.-Cyclodextrin.cntdot.6H2O and .**beta**.-**cyclodextrin**.cntdot.12H2O were transformed into **dehydrate** forms by heating at 110.degree. C for 3 h in vacuo. When the cyclodextrin **hydrate** or **dehydrate** was ground by vibrational mill, it converted from crystalline state to amorphous state. Crystallinities of intact and ground cyclodextrins were calculated by Ruland's method. In Ruland's method, as the integral upper limit affects significantly the evaluation of crystallinity. The crystallinity was determined by using continuous regions of the integral upper limit. The crystallinities and disorder parameters were determined as 83.4%, 3.2.ANG., for .alpha.-cyclodextrin.cntdot.6H2O. 87.6%, 4.3.ANG.2, for .**beta**.-**cyclodextrin**.cntdot.12H2O and 51.5%, 4.3.ANG.2 for .**beta**.-**cyclodextrin dehydrate**, respectively. The crystallinities of these 3 crystals decreased to about 8% by 3 min grinding.

=> d ibib ab kwic 31-32

L239 ANSWER 31 OF 52 USPATFULL
ACCESSION NUMBER: 93:14677 USPATFULL
TITLE: Stabilized FGF composition and production thereof
INVENTOR(S): Akiyama, Yohko, Ibaraki, Japan
Yoshioka, Minoru, Suita, Japan
Kitamori, Nobuyuki, Suita, Japan
PATENT ASSIGNEE(S): Takeda Chemical Industries, Inc., Osaka, Japan (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5189148		19930223	
APPLICATION INFO.:	US 1990-547454		19900703	(7)

	NUMBER	DATE
PRIORITY INFORMATION:	JP 1989-176228	19890707
	JP 1990-136333	19900524

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Schain, Howard E.
LEGAL REPRESENTATIVE: Conlin, David G., Williams, Gregory D.
NUMBER OF CLAIMS: 12
EXEMPLARY CLAIM: 1
LINE COUNT: 981
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Disclosed are (1) a stabilized FGF protein composition which comprises an FGF protein and water-insoluble hydroxypropyl cellulose; (2) a method for preparing a stabilized FGF protein composition, which comprises admixing an FGF protein with a water-insoluble hydroxypropyl cellulose; and (3) a method for stabilizing an FGF protein which comprises admixing an FGF protein with a water-insoluble hydroxypropyl cellulose, whereby the stabilized FGF protein can be provided. The composition is obtained in a solid state which has improved stability.
TI Stabilized FGF composition and production thereof
AB Disclosed are (1) a stabilized FGF protein composition which comprises an FGF protein and water-insoluble hydroxypropyl cellulose; (2) a method for preparing a stabilized FGF protein composition, which comprises admixing an FGF protein with a water-insoluble hydroxypropyl cellulose; and (3) a method for stabilizing an FGF protein which comprises admixing an FGF protein with a water-insoluble hydroxypropyl cellulose, whereby the stabilized FGF protein can be provided. The composition is obtained in a solid state which has improved stability.
SUMM The present invention relates to a stabilized fibroblast growth factor (hereinafter briefly referred to as FGF) protein composition, a method for preparing a stabilized FGF protein composition, and a method for stabilizing an FGF protein.
SUMM FGF was first isolated as a factor exhibiting strong growth promoting action on fibroblasts such as BALB/c3T3 cells [D. Gospodarowicz, Nature 249, 123 (1974)]. It is now known that the FGF exhibits growth promoting action on almost all cells derived from mesoblast. FGF is classified into basic FGF (hereinafter briefly referred to as bFGF) and acidic FGF (hereinafter briefly referred to as aFGF), based on the isoelectric

point thereof. bFGF and aFGF both have strong growth promoting. . .

SUMM Previously, the **FGFs** were purified to homogeneity from organs derived from animals, such as bovine pituitary. However, supply of these **FGFs** was limited, and there was a fear of antigenicity due to their heterozoic origin. Recently, there has been developed a method for producing **FGF** in large quantities. The method involves using recombinant DNA techniques to express a cloned human **FGF** gene in microorganisms or in animal cells. [FEBS Letters 213, 189-194 (1987); European Patent Publication (hereinafter also referred to as. . .

SUMM Another way of producing **FGF** in large quantity is stabilizing polypeptide producing factors using an aqueous medical composition comprising a water-soluble polysaccharides in amount sufficient. . .

SUMM Since most of the **FGF** proteins are very unstable, not only they are rapidly inactivated in aqueous solution, but also their bioactivity easily is decreased by lyophilization. Further, when the **FGF** proteins are administered for many hours as an intravenous drip, a reduction in titer during that time is unavoidable, which. . .

SUMM . . . in the cellolose chain, it is difficult to form a solid medical composition in powder when the base is an **FGF** protein. The titer of the composition is also lowered during mixing and drying process.

SUMM The present inventors have discovered that the stability of **FGF** proteins is surprisingly increased by admixing an **FGF** protein with a water-insoluble hydroxypropyl cellulose.

SUMM In particlular, the present inventors have succeeded in obtaining a solid composition having an improved stability of **FGF** protein as compared with that of the above-described aqueous medical composition comprising an **FGF** protein and water-soluble polysaccharides.

SUMM In accordance with the present invention, there is provided (1) a stabilized **FGF** protein composition which comprises an **FGF** protein and water-insoluble hydroxypropyl cellulose; (2) a method for preparing a stabilized **FGF** protein composition, which comprises admixing an **FGF** protein with a water-insoluble hydroxypropyl cellulose; and (3) a method for stabilizing an **FGF** protein, which comprises admixing an **FGF** protein with a water-insoluble hydroxypropyl cellulose.

SUMM The **FGF** proteins used in the present invention may include basic **FGF** and acidic **FGF**. The **FGF** protein used in the present invention include those derived from mammals. The mammals include human, monkey, pig, bovine, sheep and. . .

SUMM The **FGF** proteins include those extracted from various organs in which the presence of **FGFs** is already known, such as brain and pituitary.

SUMM Further, the **FGF** proteins include those obtained by the recombinant DNA technique [FEBS Letters 213, 189-194 (1987); EP Publication No. 237,966].

SUMM Hereinafter, the recombinant human basic **FGF** may be referred to as rhbFGF.

SUMM The **FGF** proteins used in the present invention include a **FGF** mutein.

SUMM Examples of the muteins of the **FGFs** used in the present invention include the muteins disclosed in Biochemical and Biophysical Research Communications 151, 701-708 (1988), EP No.. . .

SUMM For example, the **FGF** muteins used in the present invention are obtained essentially by variations of the amino acid sequences of the original peptides. . . addition of amino acid(s), deletion of constituent amino acid(s) and substitution of constituent amino acid(s) by different amino acid(s). Further, **FGF** muteins introduced by glycosylation site are included in such variations.

SUMM Such deletion of constituent amino acid(s) includes deletion of at least

one FGF-constituent amino acid.

SUMM Such substitution of constituent amino acid(s) by different amino acid(s) includes substitution of at least one FGF-constituent amino acid by at least one different amino acid.

SUMM At least one amino acid in the mutein which has at least one amino acid added to the FGF excludes methionine derived from the initiation codon used for peptide expression and a signal peptide.

SUMM The number of the added amino acid(s) is at least one. However, it may be any number as long as FGF characteristics, such as one of the characteristics of angiogenesis, cell growth stimulating activity and cell differentiating activity, are not lost.. . . More preferable amino acids include some or all of the amino acid sequences of proteins which have homology with the FGFs and which exhibit activities similar to those of the FGFs.

SUMM As for the number of the deleted FGF-constituent amino acid(s) in the mutein which lacks at least one FGF-constituent amino acid, it may be any number as long as FGF characteristics are not lost.

SUMM As for the number of FGF-constituent amino acids prior to substitution in the mutein, which has at least one FGF -constituent amino acid substituted by at least one different amino acid, it may be any number as long as FGF characteristics are not lost.

SUMM The FGF mutein has had introduced at least one glycosylation site. And the mutein may further have sugar chain(s).

SUMM The sugar which is added to a FGF mutein may be any one found in known glycosylated proteins. Examples of such sugars include N-acetyl glycosamine, N-acetyl galactosamine, mannose,. . .

SUMM (a) hybridizing a single-stranded DNA comprising a single strand of the structural gene of FGF with a mutagenic oligonucleotide primer(the above-mentioned primer is complementary to a region, including a codon for cysteine, to be replaced. . .

SUMM In the present invention, the weight ratio of the FGF protein to water-insoluble hydroxypropyl cellulose is preferably about 1:0.01 to 1,000,000, more preferably about 1:1 to 100,000, still more preferably. . .

SUMM In the present invention, the weight ratio of FGF protein to sugars, proteins, amino acids, sodium chloride and/or gum arabic is preferably about 1:0.01 to 1,000,000, more preferably about. . .

SUMM The compositions of the present invention are obtained by admixing the FGF protein with the water-insoloble hydroxypropyl cellulose, for example, by adding an aqueous solution of the FGF protein to water-insoluble hydroxypropyl cellulose in powder, followed by mixing. The pH of the aqueous solution of the FGF protein is preferably adjusted to about 3 to 10, more preferably to about 5 to 9.

SUMM . . . Pony mixer (Hosokawa Tekkosho, Japan), a Vertical granulator (Fuji Sangyo) and a Super mixer (Hosokawa Tekkosho)], by devices used for fluidized granulation [such as Glad (Okawara Seisakusho)] and by devices used for rolling granulation [such as CF (Freund)].

SUMM Sugars, proteins, amino acids, sodium chloride and/or gum arabic may be simultaneously added when water-insoluble hydroxypropyl cellulose and FGF protein are mixed, or they may be mixed with water-insoluble hydroxypropyl cellulose, followed by adding FGF protein. The production method of the composition is carried out by similar method with that of the composition comprising water-insoluble hydroxypropyl cellulose and FGF protein.

SUMM In the above mixing, the aqueous solution of the FGF protein stabilized with glucan sulfate may be used.

SUMM . . . be used. The purification can be conducted, for example, by concentrating a reaction solution containing an alkali metal salt of .

beta.-cyclodextrin sulfate, evaporating it to dryness, dissolving the condensate in water, and mixing the resulting aqueous solution with a hydrophilic solvent to separate the desired product.

SUMM . . . in toxicity to warm-blooded animals, and is therefore advantageous for parenteral or oral administration for the stabilized compositions comprising the FGF protein and the glucan sulfate.

SUMM When glucan sulfate is brought into contact with the FGF protein in aqueous media, the free glucan sulfate may be added thereto, followed by addition of a proper amount of. . .

SUMM If the FGF protein is brought into contact with glucan sulfate in aqueous media in the presence of an additional dibasic or tribasic carboxylic acid, the FGF protein is advantageously more stabilized.

SUMM When the FGF protein is brought into contact with the glucan sulfate in aqueous media, it is preferred that the glucan sulfate is. . . an amount of about 0.1 to 100 mol/mol, more preferably about 0.5 to 4 mol relative to 1 mol of FGF protein.

SUMM The concentration of the FGF protein in the aqueous media is preferably about 0.0005 to 5% by w/v, more preferably about 0.01 to 1% by. . .

SUMM Contact in the aqueous medium can be attained only by mixing the FGF protein, the glucan sulfate and the carboxylic acid as required with one another in the aqueous medium.

SUMM When the FGF protein, the glucan sulfate and the carboxylic acid as required are mixed with one another, they may be mixed as. . .

SUMM Thus, the aqueous solution of the FGF protein stabilized with glucan sulfate is obtained.

SUMM In the present invention, the above-described composition comprising FGF protein and water-insoluble hydroxypropyl cellulose may be further coated by an enteric polymer.

SUMM . . . in water or organic solvents are sprayed on the tablets, the granules or the fine grains by pan coating methods, **fluidized** coating methods, the rolling coating methods or the like. When the compositions are coated with the coating agents, it is. . .

SUMM . . . the solid composition (powder) of the present invention and fatty acid ester of polyglycerol granules can also be heated and **fluidized** to obtain granules. According to the granules, the effective ingredient (FGF protein) of the solid composition of the present invention is stably eluted and released, and stabilized for a long time.

SUMM The granulation by heating and **fluidizing** can be conducted according to conventional fluidized-bed granulating methods. The heating temperature in the granulating methods is near the melting point of the above fatty acid ester. . .

SUMM . . . the fatty acid ester of polyglycerol granules and the powder (the solid composition of the present invention) to form a **fluidized bed**, and by heating and **fluidizing** them at a required temperature. It can be confirmed by the presence or absence of the powder particles whether or. . .

SUMM As the present FGF composition is stabilized, it can be advantageously used as a medicament.

SUMM The stabilized FGF protein compositions of the present invention can be safely administered parenterally or orally to warm-blooded animals (such as human, mouse,. . .

SUMM . . . in water or organic solvents are sprayed on the tablets, the granules or the fine grains by pan coating methods, **fluidized** coating methods or rolling coating methods. The tablets, the granules and the fine grains are preferably coated at about 25.degree.. . .

SUMM The FGF protein compositions of the present invention have growth promoting action on fibroblasts, high stability and low toxicity. Therefore, the FGF protein compositions can be used as therapeutic promoting drugs for burns, traumas, postoperative tissues and the like, or therapeutic drugs. . .

SUMM When the FGF protein compositions of the present invention are used as the above-mentioned drugs, they are administered, for example, to the above-mentioned warm-blooded animals in an appropriate amount ranging from about 1 ng/kg to 100 .mu.g/kg daily as the FGF protein, taking into account the route of administration, symptoms, etc.

DETD The FGF activity in Examples described below was measured by the following method.

DETD TABLE 2

Additive	Remaining FGF Activity (%)
L-HPC	127
Lactose	8

DETD TABLE 3

Additive	Remaining FGF Activity (%)
L-HPC	85
Lactose	11

DETD . . . of the powder composition obtained in Example 4 and 95 g of L-HPC (LH-20, Shin-Etsu Chemical) were placed in a **fluidized** granulator (type FD-3S, Fuji Sangyo). Setting the supply air temperature to 54.degree. C., the mixture was heated and **fluidized**. After it was confirmed that L-HPC particles floating in a **fluidized bed** had disappeared, the supply of heat was stopped and the cooling was carried out, thereby obtaining granules.

DETD (2) 100 g of the granules of rhbFGF mutein CS23 obtained in the above item (1) was placed in the **fluidized** granulator (type FD-3S, Fuji Sangyo), and coated with a coating solution [a solution of 100 g of hydroxypropyl methyl cellulose. . .

DETD TABLE 4

Additive	Remaining FGF Activity (%)
L-HPC	100
Hydroxypropyl cellulose	44

CLM What is claimed is:

1. A stabilized FGF protein composition which comprises an FGF protein and low-substituted hydroxypropyl cellulose which contains not less than 5.0 percent and not more than 16.0 percent of hydroxypropyl. . .

2. A composition in accordance with claim 1, wherein the FGF protein is an FGF mutein.

3. A composition in accordance with claim 2, wherein the FGF protein is a mutein at least one human basic FGF-constituent amino acid of which is substituted by at least one different amino acid.

5. A method for preparing a stabilized FGF protein composition, which comprises admixing an FGF protein protein and low substituted hydroxypropyl cellulose which contains not less than

5.0 percent and mot more than 16.0 percent. . .
6. A method in accordance with claim 5, wherein the **FGF** protein is an **FGF** mutein.

7. A method in accordance with claim 6, wherein the **FGF** protein is a mutein at least one human basic **FGF**-constituent amino acid of which is substituted by at least one different amino acid.

9. A method for stabilizing an **FGF** protein, which comprises admixing an **FGF** protein and hydroxypropyl cellulose which contains not less than 5.0 percent and not more than 16.0 percent of hydroxypropyl group.

. . .
10. A method in accordance with claim 9, wherein the **FGF** protein is an **FGF** mutein.

11. A method in accordance with claim 10, wherein the **FGF** protein is a mutein at least one human basic **FGF**-constituent amino acid of which is substituted by at least one different amino acid.

L239 ANSWER 32 OF 52 USPATFULL
ACCESSION NUMBER: 92:53284 USPATFULL
TITLE: Pharmaceutical compositions having **improved dissolution** properties
INVENTOR(S): Martini, Alessandro, Milan, Italy
Torricelli, Clara, Milan, Italy
Confalonieri, Carlo, Milan, Italy
De Ponti, Roberto, Milan, Italy
PATENT ASSIGNEE(S): Farmitalia Carlo Erba S.R.L., Milan, Italy (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5126333		19920630	
APPLICATION INFO.:	US 1990-561577		19900802	(7)

	NUMBER	DATE
PRIORITY INFORMATION:	GB 1989-20135	19890906

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Griffin, Ronald W.
LEGAL REPRESENTATIVE: Oblon, Spivak, McClelland, Maier & Neustadt
NUMBER OF CLAIMS: 9
EXEMPLARY CLAIM: 1
LINE COUNT: 503
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A pharmaceutical composition comprising a drug and a dehydrated cyclodextrin having improved dissolution properties, and the process for the preparation thereof.
TI Pharmaceutical compositions having **improved dissolution** properties
DETD Operating under controlled moisture conditions 2 g of FCE 24578 /(2-cyano-3-(1,4-dihydro-1-phenyl-(1)-benzothiopyran)-(4,3-C)-pyrazol-3-yl)-3-oxo-N-phenylpropanamide).vertline. (0.0044 mol) and 5 g of **dehydrated .beta.-cyclodextrin** from Example 1 (0.0044 mol) were sieved together through a 115 m sieve and then mixed with a tumbler for 30 min. An equimolar drug/**hydrated** . **beta.-cyclodextrin** (12.15% of water in it) physical

mixture was prepared as comparison. Dissolution behaviour tests were carried out to compare each. . .

DETD TABLE 1

FCE 24578/.**beta.-cyclodextrin** physical mixtures

time (minutes)	(percent in solution) **hydrated** .beta.-CD	**dehydrated** .beta.-CD
0	0.0	0.0
15	1.0	10.5
30	2.4	10.8
45	3.7	10.1
60	5.3	10.6

DETD Operating under controlled moisture conditions 2.49 g of FCE 24304 .vertline.6-methyleneandrosta-1,4-diene-3,17-dione.vertline. (0.0084 mol) and 9.52 g of **dehydrated .beta.-cyclodextrin** from Example 1 (0.0084 mol) were sieved together through a 115 m sieve and then mixed with a tumbler for 15 min. An equimolar drug/**hydrated .beta.-cyclodextrin** physical mixture was prepared as comparison. Dissolution behaviour tests were carried out to compare each mixture. The conditions of the. . .

DETD TABLE 2

FCE 24304/.**beta.-cyclodextrin** physical mixtures

time (minutes)	(percent in solution) **hydrated** .beta.-CD	**dehydrated** .beta.-CD
0	0.0	0.0
1	3.7	6.7
3	8.4	16.0
5	12.9	23.2
10	20.8	34.2
15	27.9	41.8
30	40.7	52.4
60	54.4. . .	

DETD The same improvements were obtained using a 1:2 mol/mol ratio drug/**dehydrated .beta.-cyclodextrin** physical mixture versus an analogous **hydrated** one.

DETD TABLE 3

Medroxyprogesterone acetate/.**beta.-cyclodextrin** physical mixtures

time (minutes)	(percent in solution) **hydrated** .beta.-CD	**dehydrated** .beta.-CD
0	0.0	0.0
1	3.19	3.04
3	8.40	9.27
5	14.76	15.78
10	28.91	32.19
15	41.56	45.29
30	63.42	67.79
60	76.24. . .	

DETD The same improvements were obtained using a 1:2 mol/mol ratio drug/**dehydrated .beta.-cyclodextrin** physical mixture versus analogous **hydrated** one.

DETD TABLE 4

Temazepam/**.beta.-cyclodextrin** physical mixtures

time (minutes)	(percent in solution) **hydrated** .beta.-CD	**dehydrated** .beta.-CD
0	0.0	0.0
5	11.3	22.7
10	23.0	33.9
15	35.0	45.8
20	46.1	57.7
30	58.9	74.2
45	72.3	86.8
60	79.4	91.8

DETD Operating under controlled moisture conditions 2 g of FCE 24578 (0.0044 mol) and 5 g of **dehydrated .beta.-cyclodextrin** from Example 1 (0.0044 mol) previously premixed with a tumbler were placed in a high energy mill and ground for. . . The resulting ground composition was sieved through a 115 m sieve and then mixed with a tumbler. Two different 1:1 drug/**hydrated .beta.-cyclodextrin** co-ground compositions were made as comparison in the same operative conditions: the first one using **hydrated .beta.-cyclodextrin** as is, the other one using **hydrated .beta.-cyclodextrin** just pre-ground for 2 hours.

DETD TABLE 5

FCE 24578/**.beta.-cyclodextrin** co-ground compositions

time (minutes)	(percent in solution) **hydrated** .beta.-CD as is	**hydrated** .beta.-CD preground	dehydrated .beta.-CD
0	0.0	0.0	0.0
15	69.8	79.1	91.6
30	79.3	82.9	90.9
45	80.4	83.4	91.6
60	82.3. . .		

DETD Operating under controlled moisture conditions 2.5 g of Griseofulvin (7-chloro-2',4,6-trimethoxy-6'-methylspiro.vertline.-benzofuran-2(3H)-1'.vertline.2.vertline.cyclohexene.vertline.-3,4'-dione) (0.0070 mol) and 7.5 g of **dehydrated .beta.-cyclodextrin** from Example 1 (0.0066 mol) previously premixed were ground for 1 hour in a high energy mill. The resulting ground. . .

DETD Dissolution behaviour tests of this mixture was compared with an analogous co-ground composition with **hydrated .beta.-cyclodextrin**.

DETD TABLE 6

Griseofulvin/**.beta.-cyclodextrin** co-ground compositions

time (minutes)	(percent in solution) **hydrated** .beta.-CD	dehydrated .beta.-CD
0	0.0	0.0
5	25.3	40.4
10	35.4	52.7

15	44.0	58.3
20	50.9	61.4
30	55.5	65.3
45	60.6	68.0
60	64.6. . .	

DETD Operating under controlled moisture conditions 2.49 g of FCE 24304 (0.0084 mol) and 9.54 g of **dehydrated .beta.-cyclodextrin** from Example 1 (0.0084 mol) previously premixed with a tumbler, were placed in a high energy mill and ground for. . . and subsequently mixed with a tumbler. Dissolution behaviour tests of this mixture was compared with an analogous co-ground composition with **hydrated .beta.-cyclodextrin**. The conditions of the tests were phosphate buffer pH 7.4, 37.degree. C. and 150 rpm. The results are shown in. . .

DETD TABLE 7

FCE 24304/**.beta.-cyclodextrin** co-ground compositions

time (minutes)	(percent in solution) **hydrated** .beta.-CD	dehydrated .beta.-CD
0	0.0	0.0
1	47.0	56.7
3	69.0	78.3
5	77.3	84.2
10	84.2	89.6
15	86.3	91.0
30	89.5	93.9
60	91.7	95.9

DETD The same improvements were obtained using a 1:2 mol/mol ratio between drug and **dehydrated .beta.-cyclodextrin** co-ground composition versus an analogous one with **hydrated** B-cyclodextrin.

DETD 250 mg of an equimolecular FCE 24304/**dehydrated .beta.-cyclodextrin** physical mixture prepared according to Example 3 were **compressed** to obtain a no-disgregating disk (surface area of 1.02 cm.sup.-2). A disk of equimolecolar drg/**hydrated .beta.-cyclodextrin** physical mixture was prepared with the same force of **compression** as comparison.

DETD TABLE 8

FCE 24304/**.beta.-cyclodextrin** physical mixtures

time (minutes)	(mcg/ml) **hydrated** .beta.-CD	**dehydrated** .beta.-CD
0	0.0	0.0
2	0.49	0.69
4	0.72	1.12
6	1.06	1.52
8	1.32	1.94
10	1.71	2.24
12	1.97	2.64
14. . .		

DETD 250 mg of en equimolecular temazepam/dehydrated .beta.-CD physical mixture prepared according to Example 5, was **compressed** obtaining a non disgregating disk. Disk of equimolecular drug/hydrated .beta.-CD physical mixture was prepared with the same force of **compression** as comparison.

DETD TABLE 9

FCE Temazepam/**.beta.-cyclodextrin** physical mixtures

time (minutes)	(mcg/ml) **hydrated** .beta.-CD	**dehydrated** .beta.-CD
0	0.0	0.0
2	0.47	1.35
4	0.86	2.35
6	1.31	3.10
8	1.70	3.72
10	2.17	4.33
12	2.58	4.91

14. . .

DETD TABLE 13

Temazepam/**.beta.-cyclodextrin** compositions 1:2 m/m

time (minutes)	**hydrated** .beta.-CD (mcg/ml)	**dehydrated** .beta.-CD (mcg/ml)
5	5.3	10.7
10	9.9	18.4
15	13.9	22.3
20	17.2	25.1
30	21.6	28.6
60	28.9	33.6
90	32.2	35.4

DETD TABLE 14

Temazepam/**.beta.-cyclodextrin** compositions 1:3 m/m

time (minutes)	**hydrated** .beta.-CD (mcg/ml)	**dehydrated** .beta.-CD (mcg/ml)
5	8.0	12.1
10	12.7	17.7
15	16.0	21.0
20	19.2	23.7
30	23.4	27.2
60	31.2	33.1
90	35.3	35.4

DETD FCE 24304/**dehydrated .beta.-cyclodextrin**
(molar ratio 1:1 corresponding to 25 mg of active drug) mg 120

CLM What is claimed is:
6. A process according to claim 5 wherein the cyclodextrin is **dehydrated .beta.-cyclodextrin.**

=> d ibib ab 33

L239 ANSWER 33 OF 52 HCAPLUS COPYRIGHT 2003 ACS DUPLICATE 1
ACCESSION NUMBER: 2002:693165 HCAPLUS
DOCUMENT NUMBER: 137:218654
TITLE: Process for preparing a directly compressible .beta.-cyclodextrin and the highly compressible and

storage stable .beta.-cyclodextrin so obtained
INVENTOR(S): Lis, Jose; Lefevre, Philippe
PATENT ASSIGNEE(S): Roquette, Freres, Fr.
SOURCE: Eur. Pat. Appl., 8 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1238987	A1	20020911	EP 2002-290569	20020307
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
FR 2821844	A1	20020913	FR 2001-3156	20010308
AU 2002020325	A5	20020912	AU 2002-20325	20020305
US 2003065167	A1	20030403	US 2002-91917	20020306
JP 2002308904	A2	20021023	JP 2002-62619	20020307
CN 1375506	A	20021023	CN 2002-105428	20020308

PRIORITY APPLN. INFO.: FR 2001-3156 A 20010308
AB The .beta.-cyclodextrin useful for drug carrier, etc., is prepd. by a method comprising the steps of **dehydrating** a cyclodextrin **hydrate** compd. to a moisture content of <6%, preferably <4%, and most preferably .ltoreq.2%, then rehydrating the resulting product to a moisture content of >10%, preferably >12% and most preferably .gtoreq.13%.
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ibib ab 34

L239 ANSWER 34 OF 52 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:789450 HCAPLUS
DOCUMENT NUMBER: 137:385013
TITLE: Solid-State Phase Transition of a **Hydrated** .beta.-Cyclodextrin Dimeric Complex
AUTHOR(S): Rysanek, Nicole; Coquillay, Michel; Bourgaux, Claudie; Ollivon, Michel
CORPORATE SOURCE: Laboratoire de Physique, Faculte de Pharmacie, Universite Paris-Sud, Chatenay-Malabry, 92296, Fr.
SOURCE: Journal of Physical Chemistry B (2002), 106(45), 11870-11875
CODEN: JPCBFK; ISSN: 1520-6106
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The thermal and structural behavior of the complex .beta.-cyclodextrin 1,7-dioxaspiro[5,5]undecane.cntdot.9H2O is studied between 23 and 150.degree.C using the coupling of differential scanning calorimetry (DSC) and time-resolved X-ray diffraction as a function of temp. (XRDT). A drastic structural change between the low-temp. (LT) and the high-temp. (HT) phases, correlated with an endothermic DSC peak, shows that a solid-state phase transition takes place at about 110 .degree.C on heating. A model for the HT phase is built from the knowledge of the LT phase crystal structure and is ascertained by simulated X-ray diffraction patterns. Both LT and HT structures are columnar, and the phase transition is explained by the loss of water mols. located between the .beta.-cyclodextrin channels, leading to their close contact. The HT phase is a new structural form of the .beta.-cyclodextrin complex that is

fully **dehydrated**. The recordings of both DSC and XRDT from the same sample employed for the first time to the study of cyclodextrin phase transition allowed an unambiguous splitting of the thermal and structural evolutions and was revealed to be a very efficient tool for the monitoring of kinetically controlled processes.
REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ibib ab 35

L239 ANSWER 35 OF 52 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:491464 HCAPLUS
DOCUMENT NUMBER: 121:91464
TITLE: Improvement in the dissolution properties of theophylline with **.beta.-cyclodextrin**
AUTHOR(S): Yazan, Y.; Sumnu, M.
CORPORATE SOURCE: Anadolu Univ., Eskisehir, Turk.
SOURCE: S.T.P. Pharma Sciences (1994), 4(2), 128-32
CODEN: STSSE5; ISSN: 1157-1489
DOCUMENT TYPE: Journal
LANGUAGE: English
AB An improvement in the dissoln. of theophylline with .beta.-cyclodextrin was achieved by subjecting them to co-grinding and freeze-drying methods. The products obtained were examd. by the phase soly. method, DSC and X-ray diffractometry. The products thus prepd. were evaluated with respect to their dissoln. behavior and particle sizes, and compared with the pure drug and the phys. mixt. of theophylline and .beta.-cyclodextrin. The improvement in the dissoln. profile of theophylline in the interacted form may be due to its amorphous state, to increased wettability, or to the formation of an inclusion complex.

=> d ind 35

L239 ANSWER 35 OF 52 HCAPLUS COPYRIGHT 2003 ACS
CC 63-5 (Pharmaceuticals)
ST theophylline solubilization **beta cyclodextrin**
IT **Solubilization**
(of theophylline, by **.beta.-cyclodextrin**)
IT **Freeze drying**
(solubilization of theophylline by, with **.beta.-cyclodextrin**)
IT **Size reduction**
(grinding, solubilization of theophylline by, with **.beta.-cyclodextrin**)
IT **7585-39-9, .beta.-Cyclodextrin**
RL: BIOL (Biological study)
(solubilization of theophylline by)
IT 58-55-9, Theophylline, properties
RL: PRP (Properties)
(solubilization of, by **.beta.-cyclodextrin**)

=> d ibib ab 36

L239 ANSWER 36 OF 52 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:442578 HCAPLUS
DOCUMENT NUMBER: 121:42578

TITLE: Preparation and investigation of .**beta.**-**cyclodextrin** inclusion complex of a non-steroidal anti-inflammatory drug, tenoxicam
AUTHOR(S): Senel, S.; Cakoglu, oe.; Sumnu, M.; Duchene, D.; Hincal, A. A.
CORPORATE SOURCE: Fac. Pharm., Hacettepe Univ., Ankara, 06100, Turk.
SOURCE: Minutes Int. Symp. Cyclodextrins, 6th (1992), 397-402. Editor(s): Hedges, Allan R. Ed. Sante: Paris, Fr. CODEN: 60BCAL
DOCUMENT TYPE: Conference
LANGUAGE: English
AB A complex of tenoxicam with .beta.-cyclodextrin was prepd. by using co-grinding and freeze-drying methods. The compds. were studied by soly. method, UV and IR spectroscopy, DSC and X-ray diffractometry. Dissoln. behavior of the compds. were also examd. The dissoln. rate of tenoxicam/.beta.-cyclodextrin complexes was faster than that of the pure drug and the phys. mixt. of drug and .beta.-cyclodextrin. The enhanced dissoln. rate of the complexes might be attributed to the amorphous state, the increased wettability and the inclusion complex formation.

=> d ind 36

L239 ANSWER 36 OF 52 HCAPLUS COPYRIGHT 2003 ACS
CC 63-5 (Pharmaceuticals)
ST tenoxicam **beta cyclodextrin** inclusion complex
IT **Freeze drying**
(in prepn. of tenoxicam-**.beta.-cyclodextrin** complex)
IT **Solubilization**
(of tenoxicam, by complexation with **.beta.-cyclodextrin**)
IT Solution rate
(of tenoxicam-**.beta.-cyclodextrin** inclusion complex)
IT **Size reduction**
(grinding, in prepn. of tenoxicam-**.beta.-cyclodextrin** complex)
IT 149002-67-5
RL: BIOL (Biological study)
(formation and soly. of)
IT 59804-37-4, Tenoxicam
RL: PRP (Properties)
(soly. of, complexation with **.beta.-cyclodextrin** effect on)
IT **7585-39-9, .beta.-Cyclodextrin**
RL: BIOL (Biological study)
(tenoxicam solubilization by complexation with)

=> d ibib ab 37

L239 ANSWER 37 OF 52 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1991:435580 HCAPLUS
DOCUMENT NUMBER: 115:35580
TITLE: Effects of .**beta.-cyclodextrin** on water solubility of some steroidal hormones
AUTHOR(S): Belikov, V. G.; Kompantseva, E. V.; Gavrilin, M. V.; Dranik, L. I.
CORPORATE SOURCE: Pyatigorsk. Farm. Inst., Pyatigorsk, USSR

SOURCE: Farmatsiya (Moscow, Russian Federation) (1991), (2), 35-7
CODEN: FRMTAL; ISSN: 0367-3014
DOCUMENT TYPE: Journal
LANGUAGE: Russian
AB Inclusion complexes of steroids (hydrocortisone acetate, HA, triamcinolone acetonide, TA, and fluocinolone acetonide, FA) with .beta.-cyclodextrin were prepd. by copptn. lyophilization, grinding, and drying after vapor pressure pretreatment, and steroid soly. was evaluated. The max. soly. of HA was obsd. from complex prepd. by copptn., while that of TA and FA was better from a phys. mixt. with .beta.-cyclodextrin than from inclusion complexes. Inclusion complexation by lyophilization showed the smallest solubilizing effect. Overall, the lower steroid soly. in water, the better effect of .beta.-cyclodextrin.

=> d ind 37

L239 ANSWER 37 OF 52 HCAPLUS COPYRIGHT 2003 ACS
CC 63-5 (Pharmaceuticals)
ST **beta cyclodextrin** steroid solubilization
IT **Solubilization**
(of steroids, by **.beta.-cyclodextrin**)
IT Steroids, biological studies
RL: PRP (Properties)
(soly. of, **.beta.-cyclodextrin** effect on)
IT **Drying**
Freeze drying
(steroid-**.beta.-cyclodextrin** inclusion complexes prepn. by, drug solubilization in relation to)
IT **Size reduction**
(grinding, steroid-**.beta.-cyclodextrin** inclusion complexes prepn. by, drug solubilization in relation to)
IT 81348-57-4 81348-63-2 134767-11-6
RL: BIOL (Biological study)
(formation and drug soly. from, prepn. method effect on)
IT 50-03-3, Hydrocortisone acetate 67-73-2, Fluocinolone acetonide 76-25-5
RL: PRP (Properties)
(soly. of, **.beta.-cyclodextrin** effect on)
IT **7585-39-9, .beta.-Cyclodextrin**
RL: BIOL (Biological study)
(steroids soly. in relation to)

=> d ibib ab 38

L239 ANSWER 38 OF 52 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1990:83982 HCAPLUS
DOCUMENT NUMBER: 112:83982
TITLE: Studies on drug interaction in pharmaceutical formulations. Part XII. Solid particulates of drug-**.beta.-cyclodextrin** inclusion complexes directly prepared by a spray-drying technique
AUTHOR(S): Lin, Shan Yang; Kao, Yuh Horng
CORPORATE SOURCE: Dep. Med. Res., Veterans Gen. Hosp., Taipei, Taiwan
SOURCE: International Journal of Pharmaceutics (1989), 56(3), 249-59
CODEN: IJPHDE; ISSN: 0378-5173

DOCUMENT TYPE: Journal
LANGUAGE: English
AB Inclusion complexes of drugs (acetaminophen, indomethacin, piroxicam and warfarin) with .beta.-cyclodextrin were exptl. prepd. by using a spray-drying technique. The spray-dried products were evaluated by x-ray diffractometry, DSC, and IR spectroscopy. The micromeritic properties and dissoln. behavior of spray-dried products were examd. The spray-drying technique could be used to prep. the amorphous state of drug inclusion complexes. The flowability and compressibility of the spray-dried products were poor, due to the small particle size formed by the spray drying process. However, the dissoln. rates of drugs from tablets made by the spray-dried products were faster than those of the pure drug and the phys. mixt. of drug and .beta.-cyclodextrin. The enhanced dissoln. rate of spray-dried products might be attributed to the decreased particle size, the high-energetic amorphous state and inclusion complex formation.

=> d ind 38

L239 ANSWER 38 OF 52 HCAPLUS COPYRIGHT 2003 ACS
CC 63-5 (Pharmaceuticals)
ST cyclodextrin drug complex; spray drying cyclodextrin drug complex; solubilization drug cyclodextrin drug complex
IT Solution rate
(of drugs and their complexes and mixts. with **.beta.-cyclodextrin**)
IT **Solubilization**
(of drugs, by complexation with **.beta.-cyclodextrin**)
IT Crystal form
Flow
Particle size
(of spray-dried drugs and **.beta.-cyclodextrin**-drug complexes)
IT **Drying**
(spray, in prepn. of **.beta.-cyclodextrin**-drug complex solid particulates)
IT **7585-39-9, .beta.-Cyclodextrin**
RL: BIOL (Biological study)
(spray-dried drug properties in relation to)
IT 71299-82-6 88191-97-3 96684-39-8 105469-43-0
RL: BIOL (Biological study)
(spray-dried prepd., dissoln. and properties of)
IT 53-86-1, Indomethacin 81-81-2, Warfarin 103-90-2, Acetaminophen 36322-90-4, Piroxicam
RL: BIOL (Biological study)
(spray-dried, properties of, cyclodextrin complexes in relation to)

=> d ibib ab 39-52

L239 ANSWER 39 OF 52 SCISEARCH COPYRIGHT 2003 THOMSON ISI
ACCESSION NUMBER: 2002:535283 SCISEARCH
THE GENUINE ARTICLE: 565HG
TITLE: **Thermal** and structural characterization of commercial (alpha-, beta-, and gamma-cyclodextrins
AUTHOR: Bettinetti G (Reprint); Novak C; Sorrenti M
CORPORATE SOURCE: Univ Pavia, Dipartimento Chim Farmaceut, Via Taramelli 12, I-27100 Pavia, Italy (Reprint); Univ Pavia, Dipartimento Chim Farmaceut, I-27100 Pavia, Italy; Budapest Univ

Technol & Econ, Hungarian Acad Sci, Inst Gen & Analyt Chem, Res Grp Tech Analyt Chem, H-1111 Budapest, Hungary
COUNTRY OF AUTHOR: Italy; Hungary
SOURCE: JOURNAL OF THERMAL ANALYSIS AND CALORIMETRY, (APR-JUN 2002) Vol. 68, No. 2, pp. 517-529.
Publisher: KLUWER ACADEMIC PUBL, VAN GODEWIJCKSTRAAT 30, 3311 GZ DORDRECHT, NETHERLANDS.
ISSN: 1418-2874.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 40

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB alpha-, beta-, and gamma-cyclodextrins (CDs) marketed by five different companies were characterized from the thermal and structural point of view. Three alphaCD samples showed two-step DSC **dehydration** profiles and their XRD patterns were characteristic for alphaCD.6H(2)O form I, whereas one brand with an apparent three-step DSC **dehydration** behaviour was a mixture of alphaCD.6H(2)O form I and anhydrous alphaCD. The differences in the DSC profiles after **dehydration** and EGA onset decomposition temperatures recorded for the five betaCD brands were attributed to different manufacturing and purification **processes**. The five gammaCDs brands showed a common thermal behaviour and very similar XRD patterns. The patterns did not match the idealized pattern of gammaCD.14.1H(2)O, indicating the occurrence of two different **hydrated** crystal structures.

L239 ANSWER 40 OF 52 SCISEARCH COPYRIGHT 2003 THOMSON ISI
ACCESSION NUMBER: 2003:337529 SCISEARCH
THE GENUINE ARTICLE: 663AF
TITLE: **Energetics** of water/cyclodextrins interactions
AUTHOR: De Brauer C (Reprint); Germain P; Merlin M P
CORPORATE SOURCE: Inst Natl Sci Appl, Lab Anal Environm Procedes & Syst Ind, Batiment Sadi Carnot, 9 Rue Phys, F-69621 Villeurbanne, France (Reprint); Inst Natl Sci Appl, Lab Anal Environm Procedes & Syst Ind, F-69621 Villeurbanne, France
COUNTRY OF AUTHOR: France
SOURCE: JOURNAL OF INCLUSION PHENOMENA AND MACROCYCLIC CHEMISTRY, (DEC 2002) Vol. 44, No. 1-4, pp. 197-201.
Publisher: KLUWER ACADEMIC PUBL, VAN GODEWIJCKSTRAAT 30, 3311 GZ DORDRECHT, NETHERLANDS.
ISSN: 0923-0750.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 17

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The heat capacities of solid gamma-CD, 8.1 H2O and alpha-CD, 6.0 H2O have been measured between 10 and 300 K by adiabatic calorimetry. Using earlier results obtained in similar experiments with anhydrous cyclodextrins and with beta-CD, 9.7 H2O, a comparative analysis has been developed. The energetic behaviours of anhydrous and **hydrated** cyclodextrins (CDs) have been compared in order to investigate the role of water molecules in the stabilization of the cyclodextrin's rings and on their reactivities. Calculations, based on the additivity of thermodynamic properties, provide the energetic and entropic average contributions of water molecules in each cyclodextrin. From these results, we assumed that the water-water and water-CD interactions are rather different according to the cyclodextrin. In the (beta-CD, 9.7 H2O) structure, the water molecules seem to be better organised in a relatively independent network. Concerning **hydrated** alpha-CD and gamma-CD, stronger water-CD interactions probably prevent an optimal organisation of the water-water

bonds network. Differential scanning calorimetry was also used to follow the evolution of the thermal behaviour of gamma-CD, nH(2)O versus **hydration** ratio between 170 and 300 K. Our results indicate that the gamma-CD ring needs at least 1.6 water molecules to be stabilized in the solid state.

L239 ANSWER 41 OF 52 SCISEARCH COPYRIGHT 2003 THOMSON ISI
ACCESSION NUMBER: 96:632481 SCISEARCH
THE GENUINE ARTICLE: VD298
TITLE: DYNAMICS OF **HYDRATION** AND **DEHYDRATION** **PROCESSES** OF **BETA-CYCLODEXTRIN** **MONITORED** IN REAL-TIME BY RAMAN-SPECTROSCOPY
AUTHOR: DASILVA A M; STEINER T; SAENGER W; EMPIS J; TEIXEIRADIAS J J C (Reprint)
CORPORATE SOURCE: UNIV AVEIRO, DEPT CHEM, P-3810 AVEIRO, PORTUGAL (Reprint); UNIV AVEIRO, DEPT CHEM, P-3810 AVEIRO, PORTUGAL; POLYTECH INST COIMBRA, SCH AGR, P-3000 COIMBRA, PORTUGAL; FREE UNIV BERLIN, INST KRISTALLOG, D-14195 BERLIN, GERMANY; TECH UNIV, BIOTECHNOL LAB, P-1000 LISBON, PORTUGAL
COUNTRY OF AUTHOR: PORTUGAL; GERMANY
SOURCE: CHEMICAL COMMUNICATIONS, (21 AUG 1996) No. 16, pp. 1871-1872.
ISSN: 1359-7345.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: PHYS
LANGUAGE: ENGLISH
REFERENCE COUNT: 8
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The integrated intensity of the O-H Raman stretching band of crystalline **beta-cyclodextrin hydrate** exhibits a linear response to variations of ambient humidity for humidities > 15% and varies with temperature in a similar way as the sample thermogram; it is used to monitor, in real time, the **hydration** and **dehydration processes** which follow approximately first-order kinetics.

L239 ANSWER 42 OF 52 SCISEARCH COPYRIGHT 2003 THOMSON ISI
ACCESSION NUMBER: 95:750847 SCISEARCH
THE GENUINE ARTICLE: TB633
TITLE: **DEHYDRATION** OF THE CYCLODEXTRINS - A MODEL SYSTEM FOR THE INTERACTIONS OF **BIOMOLECULES** WITH WATER
AUTHOR: MARINI A (Reprint); BERBENNI V; BRUNI G; MASSAROTTI V; MUSTARELLI P; VILLA M
CORPORATE SOURCE: CNR, DIPARTIMENTO CHIM FIS, VIA TARAMELLI 16, I-27100 PAVIA, ITALY (Reprint); CNR, CSTE, I-27100 PAVIA, ITALY; UNIV URBINO, IST FIS, I-61029 URBINO, ITALY
COUNTRY OF AUTHOR: ITALY
SOURCE: JOURNAL OF CHEMICAL PHYSICS, (01 NOV 1995) Vol. 103, No. 17, pp. 7532-7540.
ISSN: 0021-9606.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: PHYS
LANGUAGE: ENGLISH
REFERENCE COUNT: 31
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The thermodynamics of **hydration** of biomolecules is experimentally studied in the **beta-cyclodextrin** (beta-CD), which contains water molecules in a range of configurations and has been proposed as a model system for complex biomolecules. The thermal

measurements point to the role of a structural transition from the **hydrated** beta-CD (phase I) to a ''**dehydrated**'' form (phase IT). We show that **dehydration** in phase I is assisted by a ''compensation mechanism'' for which beta-CD contributes a constant amount of energy for each H2O mole. Despite the presence of different types of H2O's, water losses in phase I:are accurately described in terms of this energy and the isosteric molar enthalpy of **dehydration** Moreover, in going from the fully **hydrated** to the fully **dehydrated** form, the contribution of beta-CD to **dehydration** is over all equal to the enthalpy of transition from phase I to phase Il. Our analysis yields the changes of an enthalpy associated with the biomolecule alone as a function of the water content. In the case of beta-CD, we can sketch a qualitative phase diagram, which assists the interpretation of details of our thermal experiments. The role of kinetic factors in the attainment of the thermodynamic equilibrium is investigated with H-2-NMR in samples recrystallized from heavy water. We find that, over a wide range of **hydration** levels, water molecules have a liquidlike diffusion, which, together with the compensation mechanism, explains the fast and nearly reversible **dehydration** of the beta-CD. (C) 1995 American Institute of Physics.

L239 ANSWER 43 OF 52 SCISEARCH COPYRIGHT 2003 THOMSON ISI
ACCESSION NUMBER: 93:601120 SCISEARCH
THE GENUINE ARTICLE: LZ394
TITLE: **THERMAL STUDY** OF WATER **BETA-CYCLODEXTRIN** INTERACTIONS
AUTHOR: MARINI A (Reprint); BERBENNI V; MASSAROTTI V; MUSTARELLI P; RICCARDI R; GAZZANIGA A; GIORDANO F; BRUNI G; VILLA M
CORPORATE SOURCE: DIPARTIMENTO CHIM FIS, VIALE TARAMELLI 16, I-27100 PAVIA, ITALY (Reprint); DIPARTIMENTO FIS A VOLTA, I-27100 PAVIA, ITALY
COUNTRY OF AUTHOR: ITALY
SOURCE: SOLID STATE IONICS, (SEP 1993) Vol. 63-5, pp. 358-362. ISSN: 0167-2738.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: PHYS
LANGUAGE: ENGLISH
REFERENCE COUNT: 8
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB It is shown that water/**beta-cyclodextrin** system has a complex behaviour above room temperature, and displays phenomena which may be separately analyzed under carefully chosen conditions: in dry **atmosphere**, and/or below 60-degrees-C, the release of water occurs much faster than the expected structural transformation from the **hydrated** to the dehydrated structure. It is argued that this transition contributes substantially to the endothermic DSC peak usually attributed to dehydration. After completing its first transition to the dehydrated structure, a water grown sample undergoes a dramatic (approximately 15%) and irreversible expansion, which apparently does not modify the crystal structure.

L239 ANSWER 44 OF 52 WPIX (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 2003-111878 [10] WPIX
DOC. NO. CPI: C2003-028578
TITLE: Preparation of **dried** modified **cyclodextrin** product with improved **dusting** and aqueous dissolution properties, comprises **drying** modified **cyclodextrin** aqueous solution and recovering **dried** modified **cyclodextrin** product.

DERWENT CLASS: D17
INVENTOR(S): SHIEH, W; SIKORSKI, C
PATENT ASSIGNEE(S): (SHIE-I) SHIEH W; (SIKO-I) SIKORSKI C; (CERE-N) CERESTAR HOLDING BV
COUNTRY COUNT: 21
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002088311	A2	20021107	(200310)*	EN	27
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR					
W: JP US					
US 2003028014	A1	20030206	(200313)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002088311	A2	WO 2002-US13037	20020423
US 2003028014	A1	US 2001-843181	20010426

PRIORITY APPLN. INFO: US 2001-843181 20010426
AB WO 200288311 A UPAB: 20030211
NOVELTY - An aqueous solution of modified **cyclodextrin** (18) is **dried** in a double-drum dryer (10) and then a **dried** modified **cyclodextrin** product with improved dusting and aqueous dissolution properties, is recovered.
DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a **dried** agglomerated modified **cyclodextrin** product. 90 weight% (wt.%) or more of the product has a particle **size** of less than 200 **microns** , and 50 wt.% or more of the product has the particle **size** of greater than 20 **microns** .
USE - For preparation of **dried** modified **cyclodextrin** product with improved dusting and aqueous dissolution properties.
ADVANTAGE - The agglomerated, modified **cyclodextrin** product is obtained by a simple and inexpensive process. The agglomerated **cyclodextrin** has excellent dissolution property in water, with low dusting problem compared to conventional spray **dried** modified **cyclodextrin**. The **cyclodextrin** product is more porous than the spray **dried** products, and has flake-shaped particles and larger particle than the spray **dried** product.
DESCRIPTION OF DRAWING(S) - The figure shows the double drum drier for **drying** aqueous solution of modified **cyclodextrin**.
Double-drum drier 10
Drums 12
Cyclodextrin aqueous solution 18
Dwg.1/6

L239 ANSWER 45 OF 52 WPIX (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 2003-074027 [07] WPIX
CROSS REFERENCE: 1998-052009 [05]; 2000-523865 [47]
DOC. NO. CPI: C2003-019200
TITLE: Production of a free flowing and **compressible** liquid/powder mixture of an active drug substance useful as sustain release formulation involves converting the drug substance into a liquisolid system.
DERWENT CLASS: A96 B07
INVENTOR(S): SPIREAS, S

PATENT ASSIGNEE(S): (SPIR-I) SPIREAS S
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 6423339	B1	20020723	(200307)*		26

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
US 6423339	B1	Div ex	US 1996-658514	19960610
		CIP of	US 1997-937240	19971001
		Cont of	US 1998-136035	19980819
			US 2000-568475	20000510

FILING DETAILS:

PATENT NO	KIND		PATENT NO
US 6423339	B1	Div ex	US 5800834
		CIP of	US 5968550
		Cont of	US 6096337

PRIORITY APPLN. INFO: US 1998-136035 19980819; US 1996-658514 19960610; US 1997-937240 19971001; US 2000-568475 20000510

AB US 6423339 B UPAB: 20030129
NOVELTY - Production of a free flowing and **compressible** liquid/powder mixture of an active drug substance involves converting the drug substance into a liquisolid system.

DETAILED DESCRIPTION - Production of a free flowing and **compressible** liquid/powder mixture of an active drug substance involves:

(a) dissolving or introducing the drug substance into a non-volatile and/or volatile liquids, to form a liquid mixture;

(b) selecting at least one powder substrate; and

(c) admixing the liquid mixture of step (a) and the powder substrate of step (b) to produce a nonadherent free-flowing and **compressible** liquid/powder mass mixture.

The amount of drug substance and powder substrate is selected to optimize flow and **compressibility**, in which the liquid-to-powder substrate ratio is 2 - 52%.

An INDEPENDENT CLAIM is included for a free-flowing and readily **compressible** liquid/powder mixture produced by converting a liquid medication into a liquisolid system involves: mixing a liquid medication with a powder substrate to produce a wet mixture, and blending the wet mixture with a coating material to produce a dry-looking, nonadherent, **compressible** liquid powder mixture. The liquid medication is a drug solution, drug suspension or liquid drug.

USE - The invention is used for producing a free flowing and **compressible** liquid/powder mixture of liquid medication (claimed).

ADVANTAGE - The method dose not involve drying or evaporation. Since non-volatile solvents can be used to prepare the drug solution or suspension, the liquid vehicle dose not evaporates. Thus, the drug is carried within the liquid system that in turn, is dispersed throughout the final product.

Dwg.0/9

L239 ANSWER 46 OF 52 WPIX (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 2000-476843 [42] WPIX
DOC. NO. CPI: C2000-143393
TITLE: **Enteric** coated particles and its preparing process.
DERWENT CLASS: B04
INVENTOR(S): CHEN, L; LIU, S; TIAN, L
PATENT ASSIGNEE(S): (ANHU-N) ANHUI PROVINCIAL HOSPITAL
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
CN 1247080	A	20000315	(200042)*		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
CN 1247080	A	CN 1999-114270	19990619

PRIORITY APPLN. INFO: CN 1999-114270 19990619
AB CN 1247080 A UPAB: 20000905
An enteric medicine in the form of particles for cleaning intestinal tract before imaging examination of abdomen and surgical and gynocologic operations, treating constipation and intestinal function recovery after operation is prepared from senna leaf, aucklandia root and green tangerine peel through steaming the aucklandia root and green tangerine peel to extract volatile oil, mixing the volatileoil with beta-**cyclodextrin** for obtaining inclusion body, reflux extracting the dregs and senna leaves by 50% alcohol with 4.0 of pH value, filtering the extracted liquid, concentrating, spray **drying**,mixing it with **microcrystal** cellulose and inclusion body, **wetting** with 90% alcohol, quickly stirring, granulating, **drying** in hot wind at 50 deg.C and coating enteric material. Obtained controlled-releasing medicine can prevent the sennoside from being damaged by strong acid in stomach and other factors for high stability and fully play the role of said medicine.
Dwg.0

L239 ANSWER 47 OF 52 WPIX (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 1999-553257 [47] WPIX
DOC. NO. NON-CPI: N1999-409606
DOC. NO. CPI: C1999-161638
TITLE: Preparing samples for storage, useful in high throughput **screens** for drugs.
DERWENT CLASS: B04 J04 S03
INVENTOR(S): HENCO, K
PATENT ASSIGNEE(S): (EVOT-N) EVOTEC BIOSYSTEMS GMBH
COUNTRY COUNT: 25
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
EP 947820	A2	19991006	(199947)*	EN	16
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI					

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
EP 947820	A2	EP 1999-103671	19990225

PRIORITY APPLN. INFO: EP 1998-105851 19980331

AB EP 947820 A UPAB: 20011203

NOVELTY - A method for sample preparation is new and comprises:

(1) combining a solution of a compound (I) with an additive or a mixture of additives; and

(2) removing the solvent in which the compound was **dissolved**

.

DETAILED DESCRIPTION - A method for sample preparation is new and comprises:

(1) combining a solution of a compound (I) with an additive or a mixture of additives;

(2) removing the solvent in which the compound was **dissolved**

.

The compound is stored and then redissolved to allow testing of the interaction between (I) and a test substance which may interact with it.

An INDEPENDENT CLAIM is also included for a multiwell container (II) which is impermeable to fluids and in which the inner surfaces of the wells are coated with an additive or a mixture of additives which have taken up or formed an inclusion complex with another compound.

USE - The new method and multiwell container may be used to perform high throughput screens (HTS) for drugs and other pharmaceutically active compounds requiring efficient release/dissolution of active ingredients in the presence of assay buffer. In addition the method and container may be used in diagnostic techniques.

ADVANTAGE - The use of **cyclodextrin** or their derivatives allows the storage of a large number of compounds with different properties for long periods of time. In contrast, prior art methods of storage which included the formation of DMSO solutions of the compounds led to their degradation over time. The compounds stored are less likely to stick to the walls of the container or to form insoluble aggregates during the **drying** process. The compounds may be easily moved around whilst stored in the container and the plate handling is simpler than that of prior art methods of storage. The deterioration rate of the stored compounds is low and the screening assay may easily be performed in aqueous solution.

The reverse transcriptase inhibitor AZT was stored in assay plates in the presence and absence of 2-hydroxypropyl- beta -**cyclodextrin**. A primer extension assay was performed in the plates on a 20-base oligo deoxynucleotide annealed to a 200 base RNA-template in the presence of buffer, dNTPs and reverse transcriptase. Primer extension was inhibited in wells which were coated in HBC and AZT, but only partially inhibited in wells not coated with HBC. The presence of HBC during **dry** storage therefore preserves the inhibitory activity of AZT.

Dwg.0/6

L239 ANSWER 48 OF 52 WPIX (C) 2003 THOMSON DERWENT

ACCESSION NUMBER: 1997-099893 [09] WPIX

DOC. NO. CPI: C1997-031873

TITLE: Water soluble beta-**carotene** prepn. - by mixing heated **cyclodextrin** soln. with beta-**carotene**-antioxidant soln. and **evapg.** to dryness.

DERWENT CLASS: B05 D13 E14

INVENTOR(S): FORTIER, N E

PATENT ASSIGNEE(S): (PROC) PROCTER & GAMBLE CO
COUNTRY COUNT: 21
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9640262	A2	19961219	(199709)*	EN	8
RW: AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE					
W: BR CA JP MX					
WO 9640262	A3	19970522	(199737)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9640262	A2	WO 1996-US6981	19960516
WO 9640262	A3	WO 1996-US6981	19960516

PRIORITY APPLN. INFO: US 1995-485328 19950607
AB WO 9640262 A UPAB: 19970228
Prepn. of water soluble beta-carotene (I) comprises: (a) preparing an aq. soln. contg. 0.5-50% **cyclodextrin** and/or its derivs. (b) heating the soln; (c) preparing a second soln. comprises at least an equiv. amt.of antioxidant to beta-carotene **dissolved** in an organic solvent; (d) adding the soln. in (c) to that in (b) with stirring to remove the organic solvent at 45-95deg.C.; (e) removing excess beta-carotene; and (f) **evapg**. to dryness. The process comprising steps. (b),(d)-(f) is claimed per se.

USE - (I) in powder form can be used in oil based prods., water based prods. and prods. contg. polyol fatty acid polyesters or other nondigestible fat substit. (I) can be used in pharmaceuticals, aq. food prods. fat substits. and prods. contg. fat substitutes.

ADVANTAGE - (I) exhibits superior resistance to oxidative and thermal degradation. The particle **size** of (I) can be reduced without affecting water soluble properties.

Dwg.0/0

L239 ANSWER 49 OF 52 WPIX (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 1997-023101 [03] WPIX
DOC. NO. CPI: C1997-007489
TITLE: Powdered hydroxy-propyl-beta-**cyclodextrin** compsn. for improving solubility and stability of pharmaceuticals, cosmetics and **agrochemicals** - has improved flow properties, **dissolves** rapidly, produces less dust and can be **compressed**
.
DERWENT CLASS: B07 C07 D21 E31
INVENTOR(S): FUERTES, P; LIS, J; SERPELLONI, M; VAPPEREAU, B
PATENT ASSIGNEE(S): (ROQF) ROQUETTE FRERES SA; (FUER-I) FUERTES P
COUNTRY COUNT: 25
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
EP 747398	A1	19961211	(199703)*	FR	9
R: AT BE CH DE DK ES FI FR GB GR IE IT LI NL PT SE					
WO 9641819	A1	19961227	(199706)	FR	23
W: AU CN HU JP KR NO					
FR 2735136	A1	19961213	(199708)		18

CA 2178668 A 19961209 (199715)
NO 9700278 A 19970122 (199716)
AU 9662298 A 19970109 (199717)
ZA 9604612 A 19970827 (199740) 21
JP 10504351 W 19980428 (199827) 17
US 5756484 A 19980526 (199828)
AU 693376 B 19980625 (199836)
HU 9700375 A2 19980528 (199838)
KR 97704787 A 19970906 (199839)
EP 747398 B1 20000927 (200048) FR
R: AT BE CH DE DK ES FI FR GB GR IE IT LI NL PT SE
DE 69610462 E 20001102 (200062)
ES 2151135 T3 20001216 (200105)
NO 310775 B1 20010827 (200157)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
EP 747398	A1	EP 1996-401211	19960606
WO 9641819	A1	WO 1996-FR856	19960606
FR 2735136	A1	FR 1995-6772	19950608
CA 2178668	A	CA 1996-2178668	19960610
NO 9700278	A	WO 1996-FR856	19960606
		NO 1997-278	19970122
AU 9662298	A	AU 1996-62298	19960606
ZA 9604612	A	ZA 1996-4612	19960604
JP 10504351	W	WO 1996-FR856	19960606
		JP 1997-502690	19960606
US 5756484	A	US 1996-657338	19960603
AU 693376	B	AU 1996-62298	19960606
HU 9700375	A2	WO 1996-FR856	19960606
		HU 1997-375	19960606
KR 97704787	A	WO 1996-FR856	19960606
		KR 1997-700788	19970205
EP 747398	B1	EP 1996-401211	19960606
DE 69610462	E	DE 1996-610462	19960606
		EP 1996-401211	19960606
ES 2151135	T3	EP 1996-401211	19960606
NO 310775	B1	WO 1996-FR856	19960606
		NO 1997-278	19970122

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9662298	A	Based on	WO 9641819
JP 10504351	W	Based on	WO 9641819
AU 693376	B	Previous Publ.	AU 9662298
		Based on	WO 9641819
HU 9700375	A2	Based on	WO 9641819
KR 97704787	A	Based on	WO 9641819
DE 69610462	E	Based on	EP 747398
ES 2151135	T3	Based on	EP 747398
NO 310775	B1	Previous Publ.	NO 9700278

PRIORITY APPLN. INFO: FR 1995-6772 19950608
AB EP 747398 A UPAB: 19990316
Powdered hydroxypropyl- beta -**cyclodextrin** compsn. contains less than 25% of 100 mu **m** particles and **dissolves** in less

than 5 mins. at 21 deg. C for a soln. contg. 20% **dry** matter (as measured in a test I).

The compsn. pref. **dissolves** in less than 3 (pref. less than 2) mins. Particles smaller than 40 mu form less than 10% of the powder, particles bigger than 315 mu form less than 40% of the powder. The flow number is 60-90, pref. 70-85. **Compressibility** is greater than 30 N, pref. greater than 100 N (evaluated in a test II).

USE - The compsn. can be used to improve the solubility and/or stability in water of active agents in powders or tablets, in pharmaceuticals, cosmetics and agrochemicals.

ADVANTAGE - The compsn. **dissolves** rapidly, and has improved flow and **compression** characteristics, cf. prior art compsns. It does not form dusts with their associated explosion risks.

Dwg.0/0

L239 ANSWER 50 OF 52 WPIX (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 1994-048553 [06] WPIX
DOC. NO. CPI: C1994-021930
TITLE: Prepn. of inclusion cpds. of **nimesulide** with **cyclodextrin**(s) - by subjecting solid mixt. aq. soln. or homogeneous slurry of **nimesulide** and water-soluble **cyclodextrin** to co-milling, spray-**drying** or kneading..
DERWENT CLASS: B04
INVENTOR(S): MAFFIONE, G
PATENT ASSIGNEE(S): (BOEH) BOEHRINGER INGELHEIM ITAL SPA
COUNTRY COUNT: 16
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9402177	A1	19940203	(199406)*	EN	16
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE					
W: AT CH DE DK ES GB LU NL PT SE					
IT 1255462	B	19951102	(199617)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9402177	A1	WO 1993-EP1560	19930618
IT 1255462	B	IT 1992-MI1833	19920728

PRIORITY APPLN. INFO: IT 1992-MI1833 19920728
AB WO 9402177 A UPAB: 19940322
Prepn. of inclusion cpds. of nimesulide with **cyclodextrin** comprises subjecting a solid mixt. an aq. soln. or a homogeneous slurry of nimesulide and water-soluble **cyclodextrin** to co-milling, to spray-**drying** or to kneading respectively.

The molar ratio of nimesulide to water-soluble **cyclodextrin** is 1:0.5 to 1:10. The water soluble **cyclodextrin** are selected from opt. substd. gamma, beta, and gamma-**cyclodextrin** or their **hydrates**.

USE/ADVANTAGE - The inclusion cpds. of nimesulide with **cyclodextrin** have analgesic and anti-inflammatory activity, a good water solubility and more efficient and rapid absorption in comparison with the uncomplexed nimesulide. The inclusion cpds. show a greater improvement of dissolution and wettability properties of nimesulide in aq. or biological media, due to the following properties, amorphous state of

the obtd. prod; surfactant-like properties of **cyclodextrin** which can reduce the interfacial tension between water-insoluble drugs and the solvent; the smaller particle **size** produced by the co-milling, spray-**drying** and kneading processes, redn. of the dissolution energy of nimesulide brought by its complete or partial amorphisation or by the transition of its original crystalline state into a higher energy state.
Dwg.0/2

L239 ANSWER 51 OF 52 WPIX (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 1995-016148 [03] WPIX
DOC. NO. CPI: C1995-007116
TITLE: **Microgranules** produced by extrusion and spheronisation - contg. cyclodextrin, useful for controlled release of medicaments or **agrochemicals**.
DERWENT CLASS: B07 C07
INVENTOR(S): FOSSATI, E; GAZZANIGA, A; GIORDANO, F; LEFEVRE, P
PATENT ASSIGNEE(S): (ROQF) ROQUETTE FRERES SA
COUNTRY COUNT: 2
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
FR 2705677	A1	19941202	(199503)*		18
IT 1265964	B	19961216	(199721)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
FR 2705677	A1	FR 1993-6430	19930528
IT 1265964	B	IT 1994-TO406	19940520

PRIORITY APPLN. INFO: FR 1993-6430 19930528
AB FR 2705677 A UPAB: 19950126
Microgranules produced by extrusion and spheronisation contain 1 **cyclodextrin** (I) as an excipient. Also claimed is the prodn. of **microgranules** by introducing (I) into a mixer, opt. together with other excipients and/or active ingredients; adding H2O and/or EtOH; extruding the mixt.; introducing the extrudates into a spheroniser to form spherical **microgranules**; and **drying** the **microgranules**.
USE - The **microgranules** are useful as carriers for pharmaceuticals, veterinary medicaments or agrochemicals.
ADVANTAGE - The **microgranules dissolve** more rapidly than those based on **microcrystalline** cellulose (MC) while still providing controlled release of active ingredients due to **cyclodextrin** clathrate formation.
Dwg.0/0

L239 ANSWER 52 OF 52 WPIX (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 1988-077394 [11] WPIX
DOC. NO. CPI: C1988-034746
TITLE: **Amorphous** inclusion complex of drug and **cyclodextrin** deriv. - prepd. by adding lipophilic drug to aq. soln. of **cyclodextrin** deriv. and freeze-**drying** or **evaporating**.
DERWENT CLASS: A96 B05

INVENTOR(S): PITHA, J
PATENT ASSIGNEE(S): (USSH) US DEPT HEALTH & HUMAN SERVICE
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 4727064	A	19880223	(198811)*		7

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 4727064	A	US 1985-738749	19850529

PRIORITY APPLN. INFO: US 1984-603839 19840425; US 1985-738749 19850529

AB US 4727064 A UPAB: 19930923
Compsns. comprising an amorphous drug/**cyclodextrin** complex is new. Prodn. of a stabilising amorphous complex of a drug and a mixt. of **cyclodextrin** comprises (i) **dissolving** an amorphous mixt. of water-soluble **cyclodextrin** derivs. capable of forming inclusion complexes with drugs in water, and (ii) solubilising lipophilic drugs in the aq. medium forming a soln. of the solubilised drug/**cyclodextrin** complex. The soln. may be freeze-**dried** or **evaporated** to give a powder of the complex.

USE/ADVANTAGE - Used for stabilising/solubilising vitamins, steroids, antiviral agents, diuretics, anticoagulants, anticonvulsants, antiinflammatory agents and spironolactone drugs, etc.. The compsns. give better drug absorption and are non-irritating and have low systemic or local toxicity. Drug solubility is increased in aq. solns. and no **microbial** contamination is observed.
0/2

=> file home
FILE 'HOME' ENTERED AT 17:46:52 ON 12 MAY 2003